(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 August 2003 (28.08.2003)

PCT

(10) International Publication Number
WO 03/070706 A1

(51) International Patent Classification[7]: C07D 231/54, 487/04, 495/04, A61K 31/416, A61P 35/02

(21) International Application Number: PCT/US03/04844

(22) International Filing Date: 19 February 2003 (19.02.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/357,960 19 February 2002 (19.02.2002) US

(71) Applicant (*for all designated States except US*): **PHARMACIA CORPORATION** [US/US]; Corporate Patent Department, P.O. Box 1027, St. Louis, MO 63006 (US).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): **XU, Xiangdong** [CN/US]; 7498 Abbey Road, Gurnee, IL 60031 (US). **CLARE, Michael** [GB/US]; 5154 West Brown Street, Skokie, IL 60077 (US). **LENNON, Patrick** [US/US]; 50 Wilshire Terrace, Webster Groves, MO 63119 (US). **METZ, Suzanne** [US/US]; 525 Westernmill Drive, Chesterfield, MO 63017 (US). **VAZQUEZ, Michael** [US/US]; 614 Castle Meadows Court, Ballwin, MO 63021 (US). **WEIER, Richard, M.** [US/US]; 240 Hickory Court, Lake Bluff, IL 60044 (US). **WOLFSON, Serge, G.** [US/US]; 15599 Hitchcock Road, Chesterfield, MO 63017 (US).

(74) Agents: **BAUER, S., Christopher** et al.; Pharmacia Corporation, Corporate Patent Dept., P.O. Box 1027, St. Louis, MO 63006 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/070706 A1

(54) **Title:** TRICYCLIC PYRAZOLE DERIVATIVES FOR THE TREATMENT OF INFLAMMATION

(57) **Abstract:** The present invention relates to substituted tricyclic pyrazole derivatives, compositions comprising such, intermediates, methods of making tricyclic pyrazole derivatives, and methods for treating cancer, inflammation, and inflammation-associated disorders, such as arthritis.

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TRICYCLIC PYRAZOLE DERIVATIVES FOR THE TREATMENT OF INFLAMMATION

FIELD OF THE INVENTION

[001] The present invention in general is in the field of anti-inflammatory pharmaceutical agents and specifically relates to substituted tricyclic pyrazole derivatives, compositions comprising them, and their use as therapeutic agents in the treatment of diseases linked to protein kinases, particularly for treating cancer, inflammation, and inflammation-associated disorders, such as arthritis.

BACKGROUND OF THE INVENTION

[002] The following description of the background of the invention is provided to aid in the understanding the invention, but is not admitted to be or describe prior art to the invention.

[003] NF-κB is a ubiquitous transcription factor that plays a prominent role in the activation of the immune system and in stress responses by regulating the transcription of many early, inducible genes including proinflammatory cytokines, adhesion molecules, growth factors, enzymes, and receptors (Ghosh S., May, M. J., and Kopp. E (1998) *Annu. Rev. Immunol.* **16**, 115-260; Zandi, E., and Karin, M. (1999) *Mol. Cell. Biol.* **19**, 4547-4551; Karin, M. (1999) *J. Biol. Chem.* **274**, 27339-27342). Specificity of gene expression is determined at a cellular level by a diverse array of external stimuli such as bacterial products including LPS, as well as cytokines, most importantly tumor necrosis factor-α (TNFα) and interleukin-β (IL1β). Through the synergistic interaction with other transcription factors, further specificity can be achieved while maintaining enormous potential to coordinately induce a large number of functionally related genes. NF-κB is composed of homo and heterodimers of the Rel protein family and is sequestered in an inactive form in the cytoplasm by members of the IκB family of inhibitory proteins (Ghosh S., May, M. J., and Kopp. E (1998) *Annu. Rev. Immunol.* **16**, 115-260; Zandi, E., and Karin,

M. (1999) *Mol. Cell. Biol.* **19**, 4547-4551; Karin, M. (1999) *J. Biol. Chem.* **274**, 27339-27342). IκBs mask the nuclear localization signal on NF-κB, preventing nuclear translocation and hence DNA binding to the promoter regions of responsive genes. Stimulation of cells with an agonist that activates NF-κB leads to a series of biochemical signals, ultimately resulting in the phosphorylation, ubiquitinylation, and degradation of IκBs, thereby releasing NF-κB for nuclear translocation (Ghosh S., May, M. J., and Kopp. E (1998) *Annu. Rev. Immunol.* **16**, 115-260; Zandi, E., and Karin, M. (1999) *Mol. Cell. Biol.* **19**, 4547-4551; Karin, M. (1999) *J. Biol. Chem.* **274**, 27339-27342). Recently, two IκB kinases (IKK1 or IKKα and IKK2 or IKKβ), which phosphorylate IκBs and thereby initiate their degradation, have been cloned and characterized by a number of laboratories (Ghosh S., May, M. J., and Kopp. E (1998) *Annu. Rev. Immunol.* **16**, 115-260; Zandi, E., and Karin, M. (1999) *Mol. Cell. Biol.* **19**, 4547-4551; Karin, M. (1999) *J. Biol. Chem.* **274**, 27339-27342). The catalytic subunits, IKK1 and IKK2, are similar structurally as well as enzymatically and exist as a heterodimer in a large protein complex referred to as the IKK signalsome (Regnier, C., Song, H., Gao, X., Goeddel, D., Cao, Z. and Rothe, M. (1997) *Cell* **90**, 373-383; DiDonato, J.A., Hayakawa, M., Rothwarf, D.M., Zandi, E. and Karin, M. (1997) *Nature* **388**, 548-554; Mercurio, F., Zhu, H., Murray, B.W., Shevchenko, A., Bennett, B.L., Li, J.W., Young, D.B., Barbosa, M., Mann, M., Manning, A. and Roa, A. (1997) *Science* **278**, 860-866; Zandi, E. Rothwarf, D.M., Delhase, M., Hayadawa, M and Karin, M. (1997) *Cell* **91**, 243-252; Woronicz, J.D., Gao, X., Cao, Z., Rothe, M. And Goeddel, D.V. (1997) *Science* **278**, 866-869). A third protein, NEMO (IKKγ, IKKAP1), is a regulatory adapter protein necessary for IKK activation and kinase activity (Yamaoka, S., Courtois, G., Bessia, C., Whiteside, S. T., Weil, R., Agou, F., Kirk, H. E., Kay, R. J., and Ireal, A. (1998) *Cell* **93**, 1231-1240; Rothwarf, D. M., Zandi, E., Natoli, G., Karin, M. (1998) *Nature* **395**, 297; Mercurio, F., Murray, B. W., Shevchenko, A., Bennet, B. L., Young, D. B., Li, J. W., Pascual, G., Motiwala, A., Zhu, H., Mann, M and Manning, A. M. (1999) *Mol. Cell. Biol.* **2**, 1526-1538). IKK1 and IKK2 are co-expressed in most human adult tissues as well as in different developmental stages of mouse embryos (Regnier, C., Song, H., Gao, X., Goeddel, D., Cao, Z. and Rothe, M. (1997) *Cell* **90**, 373-383; DiDonato, J.A., Hayakawa, M., Rothwarf,

D.M., Zandi, E. and Karin, M. (1997) *Nature* **388**, 548-554; Mercurio, F., Zhu, H., Murray, B.W., Shevchenko, A., Bennett, B.L., Li, J.W., Young, D.B., Barbosa, M., Mann, M., Manning, A. and Roa, A. (1997) *Science* **278**, 860-866; Zandi, E. Rothwarf, D.M., Delhase, M., Hayadawa, M and Karin, M. (1997) *Cell* **91**, 243-252; Woronicz, J.D., Gao, X., Cao, Z., Rothe, M. and Goeddel, D.V. (1997) *Science* **278**, 866-869; Hu, M. C. T., and Wang, Y. (1998) *Gene* **222**, 31-40). This kinase complex appears to represent a critical, common denominator in the activation of NF-κB in a number of signal transduction pathways stimulated by a variety of agonists including cytokines, such as TNFα and IL1β, microbial products such as LPS and viral proteins such as TAX, as well as phorbol esters, oxidizing agents and serine/tyrosine phosphatases (Ghosh S., May, M. J., and Kopp. E (1998) *Annu. Rev. Immunol.* **16**, 115-260; Zandi, E., and Karin, M. (1999) *Mol. Cell. Biol.* **19**, 4547-4551; Karin, M. (1999) *J. Biol. Chem.* **274**, 27339-27342).

[004] IKK1 (also termed IKKα, Regnier, C., Song, H., Gao, X., Goeddel, D., Cao, Z. and Rothe, M. (1997) *Cell* **90**, 373-383; DiDonato, J.A., Hayakawa, M., Rothwarf, D.M., Zandi, E. and Karin, M. (1997) *Nature* **388**, 548-554; Mercurio, F., Zhu, H., Murray, B.W., Shevchenko, A., Bennett, B.L., Li, J.W., Young, D.B., Barbosa, M., Mann, M., Manning, A. And Roa, A. (1997) *Science* **278**, 860-866) was cloned simultaneously by standard biochemical purification of the IκB kinase activity from TNFα stimulated HeLa S3 cells and by its interaction with the MAP3K, NF-κB inducing kinase (NIK), in a yeast two-hybrid screen. IKK1 was identified as the previously cloned serine-threonine kinase, CHUK (Connelly, M. and Marcu, K. (1995) *Cell. Mol. Biol. Res.* **41**, 537-549). IKK1 (also termed IKKα) is an 85 kDa, 745 amino acid protein that contains an N-terminal serine/threonine kinase catalytic domain, a leucine zipper-like amphipathic helix, and a C-terminal helix-loop-helix domain. IKK2 (also termed IKKβ) was also cloned by standard biochemical purification, copurifying with IKK1 from TNFα stimulated HeLa S3 cells as well as by being identified in the public database from an EST clone with sequence homology to IKK1 (Mercurio, F., Zhu, H., Murray, B.W., Shevchenko, A., Bennett, B.L., Li, J.W., Young, D.B., Barbosa, M., Mann, M., Manning, A. and Roa, A. (1997) *Science* **278**, 860-866; Zandi, E. Rothwarf,

D.M., Delhase, M., Hayadawa, M and Karin, M. (1997) *Cell* **91**, 243-252; Woronicz, J.D., Gao, X., Cao, Z., Rothe, M. And Goeddel, D.V. (1997) *Science* **278**, 866-869). IKK2 is an 87 kDa, 756 amino acid protein with the same over all topology as IKK1 except for the addition of an 11 amino acid extension at the C-terminus. IKK1 and IKK2 are 52% identical overall with 65% identity in the kinase domain and 44% identity in the protein interaction domains in the C-terminus. Data obtained using transient mammalian expression analysis, by *in vitro* translation experiments and by coexpression in a baculoviral system reveals that IKK1 and IKK2 associate preferentially as a heterodimer through their leucine zipper motifs. Although homodimers have also been described in these systems, the heterodimer is thought to be the physiologic form of the kinase in mammalian cells (Zandi, E. Rothwarf, D.M., Delhase, M., Hayadawa, M and Karin, M. (1997) *Cell* **91**, 243-252; Li, J., Peet, G.W., Pullen, S.S., Schembri-King, J., Warren, T.C., Marcu, K.B., Kehry, M.R., Barton, R. and Jakes, S. (1998) *J. Biol. Chem.* **273**, 30736-30741). Finally, NEMO (also termed IKKγ) contains three α-helical regions including a leucine zipper, interacts preferentially with IKK2 and is required for activation of the heterodimeric kinase complex perhaps by bringing other proteins into the signalsome complex (Yamaoka, S., Courtois, G., Bessia, C., Whiteside, S. T., Weil, R., Agou, F., Kirk, H. E., Kay, R. J., and Ireal, A. (1998) *Cell* **93**, 1231-1240; Rothwarf, D. M., Zandi, E., Natoli, G., Karin, M. (1998) *Nature* **395**, 297; Mercurio, F., Murray, B. W., Shevchenko, A., Bennet, B. L., Young, D. B., Li, J. W., Pascual, G., Motiwala, A., Zhu, H., Mann, M and Manning, A. M. (1999) *Mol. Cell. Biol.* **2**, 1526-1538).

[005] The kinase activities of IKK1 and IKK2 are regulated by phosphorylation and require an intact leucine zipper (LZ) for dimerization as well as an intact helix-loop-helix (HLH) domain, which can exert a positive regulatory effect on kinase activity even when it is expressed in trans with the remainder of the IKK protein (Regnier, C., Song, H., Gao, X., Goeddel, D., Cao, Z. and Rothe, M. (1997) *Cell* **90**, 373-383; DiDonato, J.A., Hayakawa, M., Rothwarf, D.M., Zandi, E. and Karin, M. (1997) *Nature* **388**, 548-554; Mercurio,F., Zhu, H., Murray, B.W., Shevchenko, A., Bennett, B.L., Li, J.W., Young, D.B., Barbosa, M., Mann, M.,

Manning, A. and Roa, A. (1997) *Science* **278**, 860-866; Zandi, E. Rothwarf, D.M., Delhase, M., Hayadawa, M and Karin, M. (1997) *Cell* **91**, 243-252; Woronicz, J.D., Gao, X., Cao, Z., Rothe, M. and Goeddel, D.V. (1997) *Science* **278**, 866-869; Dehase, M., Hayakawa, M., Chen, Y., and Karin, M. (1999) *Science* **284**, 309-313). Both IKK subunits contain a canonical MAPKK activation loop motif near the N-terminus which is the target for phosphorylation and activation of kinase activity by MAP3Ks such as NIK and MEKK1, although the physiologic regulation by these two upstream kinases awaits further characterization (Zandi, E., and Karin, M. (1999) *Mol. Cell. Biol.* **19**, 4547-4551; Karin, M. (1999) *J. Biol. Chem.* **274**, 27339-27342; Karin, M., and Delhase, M. (1998) *Proc. Natl. Acad. Sci.* USA **95**, 9067-9069). Finally, phosphorylation of serines in the C-terminus of IKK2 results in a decrease in IKK activity and it is postulated to be responsible for the transient kinase activity seen after stimulation of cells with an agonist (Dehase, M., Hayakawa, M., Chen, Y., and Karin, M. (1999) *Science* **284**, 309-313).

[006] IKK2 demonstrates a more potent kinase activity compared to IKK1 using IκBα or IκBβ as a substrate (Mercurio, F., Zhu, H., Murray, B.W., Shevchenko, A., Bennett, B.L., Li, J.W., Young, D.B., Barbosa, M., Mann, M., Manning, A. and Roa, A. (1997) *Science* **278**, 860-866; Zandi, E. Rothwarf, D.M., Delhase, M., Hayadawa, M and Karin, M. (1997) *Cell* **91**, 243-252; Woronicz, J.D., Gao, X., Cao, Z., Rothe, M. and Goeddel, D.V. (1997) *Science* **278**, 866-869; Dehase, M., Hayakawa, M., Chen, Y., and Karin, M. (1999) *Science* **284**, 309-313). Mutations of the phospho-acceptor serine residues within the MAPKK activation loop alters IKK2 kinase activity; the serine to alanine substitutions result in decreased kinase activity whereas the serine to glutamic acid substitutions result in a constitutively active kinase. Similar alanine mutations in IKK1 do not result in a decreased stimulation of total IKK activity in response to TNFα or IL1β (Dehase, M., Hayakawa, M., Chen, Y., and Karin, M. (1999) *Science* **284**, 309-313). IKK2 being the dominant kinase activity within the IKK complex is further supported by the analysis of fibroblasts from mice deficient in IKK1 or IKK2. Fibroblasts lacking IKK1 retain full IKK activity in response to cytokines and could activate NF-κB. In contrast, fibroblasts lacking IKK2 do not exhibit IKK activity when

stimulated with cytokines nor do they activate NF-κB. Furthermore, the phenotypes of each IKK knock out is unique with IKK1 deficiency resulting in skin and skeletal defects and IKK2 knock out being embryonic lethal due to hepatocyte apoptosis (Li, Q., Antwerp, D. V., Mercurio, F., Lee, K., and Verma, I. M. (1999) *Science* **284**, 321-325; Takeda, K., Tekeuchi, O., Tsujimura, T., Itami, S., Adachi, O., Kawai, T., Sanjo, H., Yoshikawa, K., Terada, N, and Akira, S. (1999) *Science* **284**, 313-316; Hu, Y., Baud, V., Delhase, M., Zhang, P., Deerinck, T., Ellisman, M., Johnson, R., and Karin, M. (1999) *Science* **284**, 315-320; Li, Q., Lu, Q., Hwang, J. Y., Buscher, D., Lee, K., Izpisua-Belmonte, J. C., and Verma, I. M. (1999) *Gene and Development* **13**, 1322-1328; Tanaka, M., Fuentes, M. E., Yamaguchi, K., Durnin, M. H., Dalrymple, S. A., Hardy, K. L., and Goeddel, D. V. (1999) *Immunity* **10**, 421-429).

[007] It is well-known that NF-KB plays a key role in the regulated expression of a large number of pro-inflammatory mediators including cytokines such as IL-6 and IL-8, cell adhesion molecules, such as ICAM and VCAM, and inducible nitric oxide synthase (iNOS). Such mediators are known to play a role in the recruitment of leukocytes at sites of inflammation and in the case of iNOS, may lead to organ destruction in some inflammatory and autoimmune diseases. The importance of NF-κB in inflammatory disorders is further strengthened by studies of airway inflammation including asthma in which NF-κB has been shown to be activated. This activation may underlie the increased cytokine production and leukocyte infiltration characteristic of these disorders. In addition, inhaled steroids are known to reduce airway hyperresponsiveness and suppress the inflammatory response in asthmatic airways. In light of the recent findings with regard to glucocorticoid inhibition of NF-κB, one may speculate that these effects are mediated through an inhibition of NF-κB. Further evidence for a role of NF-κB in inflammatory disorders comes from studies of rheumatoid synovium. Although NF-κB is normally present as an inactive cytoplasmic complex, recent immunohistochemical studies have indicated that NF-κB is present in the nuclei, and hence active, in the cells comprising rheumatoid synovium. Furthermore, NF-κB has been shown to be activated in human synovial cells in response to stimulation with TNF-α. Such a

distribution may be the underlying mechanism for the increased cytokine and eicosanoid production characteristic of this tissue. See Roshak, A. K., et al., J. Biol. Chem., 271, 31496-31501 (1996).

[008] NF-κB in inflammatory disorders is further strengthened by studies of airway inflammation including asthma in which NF-κB has been shown to be activated. This activation may underlie the increased cytokine production and leukocyte infiltration characteristic of these disorders. In addition, inhaled steroids are known to reduce airway hyper responsiveness and suppress the inflammatory response in asthmatic airways. In light of the recent findings with regard to glucocorticoid inhibition of NF-κB, one may speculate that these effects are mediated through an inhibition of NF-κB. Further evidence for a role of NF-κB in inflammatory disorders comes from studies of rheumatoid synovium. Although NF-κB is normally present as an inactive cytoplasmic complex, recent immunohistochemical studies have indicated that NF-κB is present in the nuclei, and hence active, in the cells comprising rheumatoid synovium. Furthermore, NF-κB has been shown to be activated in human synovial cells in response to stimulation with TNF-α. Such a distribution may be the underlying mechanism for the increased cytokine and eicosanoid production characteristic of this tissue. See Roshak, A. K., et al., J. Biol. Chem., 271, 31496-31501 (1996).

[009] The NF-κB/Rel and IκB proteins are also likely to play a key role in neoplastic transformation. Family members are associated with cell transformation in vitro and in vivo because of overexpression, gene amplification, gene rearrangements, or translocations (Gilmore TD, *Trends Genet* **7**:318-322, 1991; Gillmore TD, *Oncogene* **18**:6925-6937, 1999; Rayet B. et al., *Oncogene* **18**: 6938-6947, 1991). In addition, rearrangement and/or amplification of the genes encoding these proteins are seen in 20-25% of certain human lymphoid tumors. In addition, a role for NF-κB in the regulation of apoptosis, cell cycle progression, invasion, and metastasis has been reported (Bours V. et al., *Biochemical Pharmacology* **60**:1085-1090, 2000) strengthening the role of this transcription factor in the control of cell proliferation. The inhibition of NF-κB has been shown to potentiate TNF- and

cancer therapy through increased apoptosis (Wang C-Y et al., *Science* **274**:784-787, 1996; Wang C-Y et al., *Nat Med* **5**:412-417, 1999). It has also been shown that human T-cell leukemia virus type 1 (HTLV1) infected cells (the etiological agent of an aggressive malignancy of activated CD4$^+$ T lymphocytes), IKKα and IKKβ are expressed constitutively, which normally function in a transient manner (Chu Z-L et al., *J of Biological Chemistry* **273**:15891-15894, 1998). The HTLV1 transforming and transactivating protein (Tax) has been shown to bind MEKK1 and increases the activity of IKKβ to enhance phosphorylation of serine residues in IκBα that lead to its degradation.

[0010] Pyrazoles have been described for use in the treatment of inflammation. U.S. Patent No. 5,134,142 to Matsuo et al describes 1,5-diaryl pyrazoles, and specifically, 1-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3-trifluoromethyl pyrazole, as having anti-inflammatory activity.

[0011] U.S. Patent No. 3,940,418 to R. Hamilton describes tricyclic 4,5-dihydrobenz[g]indazoles as antiinflammatory agents. In addition, R. Hamilton [*J. Heterocyclic Chem.*, **13**, 545 (1976)] describes tricyclic 4,5-dihydrobenz[g]indazoles as antiinflammatory agents. U.S. Patent No. 5,134,155 describes fused tricyclic pyrazoles having a saturated ring bridging the pyrazole and a phenyl radical as HMG-CoA reductase inhibitors. European publication EP 477,049, published Mar. 25, 1992, describes [4,5-dihydro-1-phenyl-1H-benz[g]indazol-3-yl]amides as having antipsychotic activity. European publication EP 347,773, published Dec. 27, 1989, describes [4,5-dihydro-1-phenyl-1H-benz[g]indazol-3-yl]propanamides as immunostimulants. M. Hashem et al [*J. Med. Chem.*, **19**, 229 (1976)] describes fused tricyclic pyrazoles, having a saturated ring bridging the pyrazole and a phenyl radical, as antibiotics.

[0012] Certain substituted pyrazolyl-benzenesulfonamides have been described in the literature as synthetic intermediates. Specifically, 4-[5-(4-chlorophenyl)-3-phenyl-1*H*-pyrazol-1-yl]benzenesulfonamide has been prepared from a pyrazoline compound as an intermediate for compounds having hypoglycemic activity [R.

Soliman et al, *J. Pharm. Sci.*, **76**, 626 (1987)]. 4-[5-[2-(4-Bromophenyl)-2*H*-1,2,3-triazol-4-yl]-3-methyl-1*H*-pyrazol-1-yl]benzenesulfonamide has been prepared from a pyrazoline compound and described as potentially having hypoglycemic activity [H. Mokhtar, *Pak. J. Sci. Ind. Res.*, **31**, 762 (1988)]. Similarly, 4-[4-bromo-5-[2-(4-chlorophenyl)-2*H*-1,2,3-triazol-4-yl]-3-methyl-1*H*-pyrazol-1-yl]benzenesulfonamide has been prepared [H. Mokhtar et al, *Pak. J. Sci. Ind. Res.*, **34**, 9 (1991)].

[0013] The phytotoxicity of pyrazole derivatives is described [M. Cocco et al, *Il. Farmaco-Ed. Sci.*, **40**, 272 (1985)], specifically for 1-[4-(aminosulfonyl)phenyl]-5-phenyl-1H-pyrazole-3,4-dicarboxylic acid.

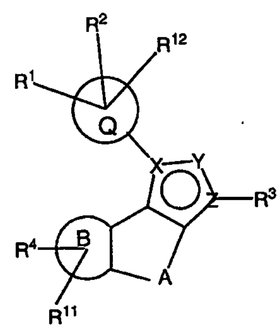
[0014] The use of styryl pyrazole esters for antidiabetes drugs is described [H. Mokhtar et al, *Pharmazie*, **33**, 649-651 (1978)]. The use of styryl pyrazole carboxylic acids for antidiabetes drugs is described [R. Soliman et al, *Pharmazie*, **33**, 184-5 (1978)]. The use of 4-[3,4,5-trisubstituted-pyrazol-1-yl]benzenesulfonamides as intermediates for sulfonylurea anti-diabetes agents is described, and specifically, 1-[4-(aminosulfonyl)phenyl]-3-methyl-5-phenyl-1*H*-pyrazole-4-carboxylic acid [R. Soliman et al, *J. Pharm. Sci.*, **72**, 1004 (1983)]. A series of 4-[3-substituted methyl-5-phenyl-1*H*-pyrazol-1-yl]benzenesulfonamides has been prepared as intermediates for anti-diabetes agents, and more specifically, 4-[3-methyl-5-phenyl-1*H*-pyrazol-1-yl]benzenesulfonamide [H. Feid-Allah, *Pharmazie*, **36**, 754 (1981)]. In addition, 1-(4-[aminosulfonyl]phenyl)-5-phenylpyrazole-3-carboxylic acid has been prepared from the above described 4-[3-methyl-5-phenyl-1*H*-pyrazol-1-yl]benzenesulfonamide compound [R. Soliman et al, *J. Pharm. Sci.*, **70**, 602 (1981)].

[0015] WO 00/27822 discloses tricyclic pyrazole derivatives, WO 00/59901 discloses dihydroindeno pyrazoles, WO 95/15315 discloses diphenyl pyrazole compounds, WO 95/15317 discloses triphenyl pyrazole compounds, WO 95/15318 discloses tri-substituted pyrazole compounds, and WO 96/09293 discloses benz[g]indazolyl derivatives.

[0016] WO 95/15316 discloses substituted pyrazolyl benzenesulfamide derivatives.

DETAILED DESCRIPTION OF THE INVENTION

[0017] A class of compounds, which are useful in treating cancer, inflammation, and inflammation related disorders, is defined by Formula I:



wherein

A is selected from the group consisting of: $(CH_2)_m$ and $(CH_2)_n$-CH=CH-$(CH_2)_n$; wherein each CH_2 may be independently substituted with one or more substitution selected from the group consisting of: hydroxy, halo, alkoxy, lower alkyl, amino, aminoalkyl, alkylamino, alkenyl, and alkynyl;

m is 0 to 8;

n is independently selected from 0, 1 or 2;

Q is a 5 or 6 membered heteroaryl, or aryl, optionally saturated, or optionally substituted with R^1, R^2, or R^{12};

B is an aromatic heterocyclic;

X is selected from the group consisting of: N and C;

Y and **Z** are independently selected from the group consisting of: N, C, CH, CR^3, S, and O;

$\mathbf{R^1}$ is selected from the group consisting of: hydrido, halogen, alkyl, aryl, heteroaryl, alkenyl, alkynyl, haloalkyl, CN, NO_2, OR^5, $OCOOR^5$, CO_2R^7,

$CON(R^6)R^7$, COR^6, SR^6, SOR^6, SO_2R^6, NR^6R^7, NR^6COR^7, NR^6CONHR^7, $NR^6SO_2R^7$, $NR^6SO_2NHR^7$, and $SO_2N(R^6)R^7$ wherein R^6 and R^7 may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from the group consisting of: S, SO, SO_2, O, and NR^6; wherein said alkenyl, alkynyl, alkyl, aryl, heteroaryl or OR^5 are optional substituted with, hydrido, halogen, alkyl, hydroxyalkyl, aryl, heteroaryl, haloalkyl, $COCF_3$, CN, NO_2, OR^5, $OCOOR^5$, CO_2R^7, $CON(R^6)R^7$, COR^6, SR^6, SOR^6, SO_2R^6, NR^6R^7, NR^6COR^7, NR^6CONHR^7, $NR^6SO_2R^7$, $NR^6SO_2NHR^7$, and $SO_2N(R^6)R^7$ wherein R^6 and R^7 may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from the group consisting of: S, SO, SO_2, O, and NR^6;

$\mathbf{R^2}$ is selected from the group consisting of: halogen, hydrido, hydroxyalkyl, alkyl, OR^6, CN, NO_2, SR^6, NHR^6, $CON(R^6)R^7$, $NHCONHR^6$, CO_2H, and haloalkyl;

$\mathbf{R^1}$ and $\mathbf{R^2}$ may be taken together to form a 5 to 7 membered saturated or unsaturated carbocyclic ring optionally containing 0 to 3 heteroatoms selected from the group consisting of: N, O, or S, and wherein said ring is optionally substituted with R^1;

$\mathbf{R^3}$ is selected from the group consisting of: substituted or unsubstituted amidine, alkylamino, aminoalkyl, $CONHR^{16}$, NH_2, $NHCOR^6$, and CH_2NHCOR^6;

$\mathbf{R^4}$ is selected from the group consisting of: halogen, alkylsulfinyl, alkylsulfonyl, cyano, alkoxycarbonyl, alkyl, haloalkyl, hydrido, hydroxyalkyl, haloalkoxy, heterocyclic, nitro, acylamino, aryl, heteroaryl, and alkenyl, OR^{13}, SR^8, $SO_2N(R^8)R^{8'}$, NHR^9, $NHCOR^9$, NR^9COR^9, $NHCO(OR^9)$, $NR^9CO(OR^9)$, $NR^8SO_2R^{10}$, $NHSO_2N(R^{10})R^{10'}$, $NR^6CON(R^{10})R^{10'}$, COR^9, CO_2R^8, $CON(R^8)R^{8'}$, wherein R^8 and $R^{8'}$ may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from S, SO, SO_2, O, N, and NR^6, and wherein R^{10} and $R^{10'}$ may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted

heteroatoms selected from S, SO, SO_2, O, N, and NR^6 wherein said aryl, heterocyclic, heteroaryl, or alkenyl are optionally substituted with R^9;

R^5 is selected from the group consisting of: hydrido, alkyl, aryl, arylalkyl, heteroaryl, heterocyclicalkyl, and heteroarylalkyl, wherein aryl, alkyl, arylalkyl, heteroaryl, heterocyclicalkyl, or heteroarylalkyl are optionally substituted with one or more radicals selected from the group consisting of: OR^{14}, $N(R^{14})R^{14'}$, and glycols;

R^6 is independently selected from the group consisting of: hydrido, aryl, heteroaryl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, heterocyclicalkyl, and heterocyclic;

R^7 is independently selected from the group consisting of: hydrido, aryl, heteroaryl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, heterocyclicalkyl, and heterocyclic;

R^8 is independently selected from the group consisting of: hydrido, aryl, heteroaryl, arylalkyl, heterocyclic, haloalkyl, arylalkylamino, alkylaminoalkyl, dialkylaminoalkyl, alkyl, alkenyl, alkynyl, heteroarylalkyl, and heterocyclicalkyl;

$R^{8'}$ is independently selected from the group consisting of: hydrido, aryl, heteroaryl, arylalkyl, heterocyclic, haloalkyl, arylalkylamino, alkylaminoalkyl, dialkylaminoalkyl, alkyl, alkenyl, alkynyl, heteroarylalkyl, and heterocyclicalkyl;

R^9 is independently selected from the group consisting of: hydrido, lower alkyl, aryl, heteroaryl, arylalkyl, heterocyclic, cycloalkyl, heterocyclicalkyl, haloalkyl, arylalkylamino, amino, aminoalkyl, aminoacyl, nitro, azido, and heteroarylalkyl, wherein alkyl, aryl, heteroaryl, aminoalkyl, or arylalkyl are optionally substituted with one or more radical selected from the group consisting of: alkylsulfonamide, sulfamyl, alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, aminoalkyl, alkylaminoalkyl, alkoxy, halogen, acyloxy, oxy, formyl, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, nitro, azido, benzyloxy, dialkylaminoacyl,

thioalkyl, aminoacyloxy, thiocyanate, isothiocyanate, alkyldioxy, hydroxyalkyl, alkylamino, alkyloxycarbonyl, alkoxyalkyl, alkenylamino, alkynylamino, alkenyl, alkynyl, dialkylaminoalkyloxy, and heterocyclic optionally substituted with alkyl, alkylamino, aminoalkyl, hydroxyalkyl, and alkylaminoalkyl;

R^{10} is independently selected from the group consisting of: hydrido, lower alkyl, heteroaryl, heterocyclic, haloalkyl, arylalkylamino, heteroarylalkyl, aryl, and arylalkyl, wherein aryl, heteroaryl, heterocyclic, or arylalkyl are optionally substituted with one or more radical selected from alkyl, alkoxy, halogen, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, benzyloxy, dialkylaminoalkyloxy, and heterocyclic,

$R^{10'}$ is independently selected from the group consisting of: hydrido, lower alkyl, heteroaryl, heterocyclic, haloalkyl, arylalkylamino, heteroarylalkyl, aryl, and arylalkyl, wherein aryl, heteroaryl, heterocyclic, or arylalkyl are optionally substituted with one or more radical selected from alkyl, alkoxy, halogen, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, benzyloxy, dialkylaminoalkyloxy, and heterocyclic,

R^{11} is selected from the group consisting of: hydrido, halogen, haloalkyl, CN, CO_2R^5, lower alkyl, lower alkenyl, lower alkynyl, alkoxy, and $CONH_2$;

R^{12} is selected from the group consisting of: hydrido, halogen, alkyl, and alkoxy;

R^{13} is selected from the group consisting of: hydrido, alkyl, aryl, arylalkyl, heteroaryl, heterocyclicalkyl, and heteroarylalkyl, wherein aryl, alkyl, arylalkyl, heteroaryl, heterocyclicalkyl, or heteroarylalkyl are optionally substituted with one or more radicals selected from the group consisting of: OR^{14}, $N(R^{14})R^{14'}$, and glycols;

R^{14} is independently selected from the group consisting of: hydrido, and lower alkyl;

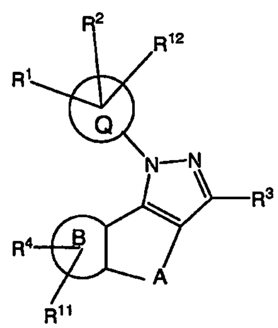
$R^{14'}$ is independently selected from the group consisting of: hydrido, and lower alkyl;

R^{15} is selected from the group consisting of: hydrido, halogen, alkyl, cycloalkyl, aryl, haloalkyl, heteroaryl, heterocyclic, alkylalkene, alkylalkyne, hydroxy, hydroxyalkyl, alkylhydroxy, amino, aminoalkyl, alkylamino, alkylaminoalkyl, alkylhydroxyalkyl, nitro, cyano, alkylthio, alkylsulfinyl, and alkylsulfonyl; wherein aryl or arylalkyl are optionally substituted with one or more radical selected from alkyl, alkoxy, halo, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, benzyloxy, dialkylaminoalkyloxy, heterocyclic; and

R^{16} is independently selected from the group consisting of: hydrido, aryl, arylalkyl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkoxy, and alkoxyalkyl;

or isomers, tautomers, carriers, esters, prodrugs, pharmaceutically acceptable salts thereof.

[0018] Another class of compounds is defined by formula II



wherein

A is selected from the group consisting of: $(CH_2)_m$ and $(CH_2)_n$-CH=CH-$(CH_2)_n$; wherein each CH_2 may be independently substituted with one or more substitution selected from the group consisting of: hydroxy, halo, alkoxy, lower alkyl, amino, aminoalkyl, alkylamino, alkenyl, and alkynyl;

m is 0 to 8;

n is independently selected from 0, 1, or 2;

Q is a 5 or 6 membered heteroaryl, or aryl, optionally saturated, or optionally substituted with R^1, R^2, or R^{12};

B is an aromatic heterocyclic;

$\mathbf{R^1}$ is selected from the group consisting of: hydrido, halogen, alkyl, aryl, heteroaryl, alkenyl, alkynyl, haloalkyl, CN, NO_2, OR^5, $OCOOR^5$, CO_2R^7, $CON(R^6)R^7$, COR^6, SR^6, SOR^6, SO_2R^6, NR^6R^7, NR^6COR^7, NR^6CONHR^7, $NR^6SO_2R^7$, $NR^6SO_2NHR^7$, and $SO_2N(R^6)R^7$ wherein R^6 and R^7 may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from the group consisting of: S, SO, SO_2, O, and NR^6; wherein said alkenyl, alkynyl, alkyl, aryl, heteroaryl or OR^5 are optional substituted with, hydrido, halogen, alkyl, hydroxyalkyl, aryl, heteroaryl, haloalkyl, $COCF_3$, CN, NO_2, OR^5, $OCOOR^5$, CO_2R^7, $CON(R^6)R^7$, COR^6, SR^6, SOR^6, SO_2R^6, NR^6R^7, NR^6COR^7, NR^6CONHR^7, $NR^6SO_2R^7$, $NR^6SO_2NHR^7$, and $SO_2N(R^6)R^7$ wherein R^6 and R^7 may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from the group consisting of: S, SO, SO_2, O, and NR^6;

$\mathbf{R^2}$ is selected from the group consisting of: halogen, hydrido, hydroxyalkyl, alkyl, OR^6, CN, NO_2, SR^6, NHR^6, $CON(R^6)R^7$, $NHCONHR^6$, CO_2H, and haloalkyl;

$\mathbf{R^1}$ and $\mathbf{R^2}$ may be taken together to form a 5 to 7 membered saturated or unsaturated carbocyclic ring optionally containing 0 to 3 heteroatoms selected from the group consisting of: N, O, or S, and wherein said ring is optionally substituted with R^1;

$\mathbf{R^3}$ is selected from the group consisting of: substituted or unsubstituted amidine, alkylamino, aminoalkyl, $CONHR^{16}$, NH_2, $NHCOR^6$, and CH_2NHCOR^6;

$\mathbf{R^4}$ is selected from the group consisting of: halogen, alkylsulfinyl, alkylsulfonyl, cyano, alkoxycarbonyl, alkyl, haloalkyl, hydrido, hydroxyalkyl, haloalkoxy, heterocyclic, nitro, acylamino, aryl, heteroaryl, and alkenyl, OR^{13}, SR^8, $SO_2N(R^8)R^{8'}$, NHR^9, $NHCOR^9$, NR^9COR^9, $NHCO(OR^9)$, $NR^9CO(OR^9)$, $NR^8SO_2R^{10}$, $NHSO_2N(R^{10})R^{10'}$,

$NR^6CON(R^{10})R^{10'}$, COR^9, CO_2R^8, $CON(R^8)R^{8'}$, wherein R^8 and $R^{8'}$ may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from S, SO, SO_2, O, N, and NR^6, and wherein R^{10} and $R^{10'}$ may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from S, SO, SO_2, O, N, and NR^6 wherein said aryl, heterocyclic, heteroaryl, or alkenyl are optionally substituted with R^9;

R^5 is selected from the group consisting of: hydrido, alkyl, aryl, arylalkyl, heteroaryl, heterocyclicalkyl, and heteroarylalkyl, wherein aryl, alkyl, arylalkyl, heteroaryl, heterocyclicalkyl, or heteroarylalkyl are optionally substituted with one or more radicals selected from the group consisting of: OR^{14}, $N(R^{14})R^{14'}$, and glycols;

R^6 is independently selected from the group consisting of: hydrido, aryl, heteroaryl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, heterocyclicalkyl, and heterocyclic;

R^7 is independently selected from the group consisting of: hydrido, aryl, heteroaryl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, heterocyclicalkyl, and heterocyclic;

R^8 is independently selected from the group consisting of: hydrido, aryl, heteroaryl, arylalkyl, heterocyclic, haloalkyl, arylalkylamino, alkylaminoalkyl, dialkylaminoalkyl, alkyl, alkenyl, alkynyl, heteroarylalkyl, and heterocyclicalkyl;

$R^{8'}$ is independently selected from the group consisting of: hydrido, aryl, heteroaryl, arylalkyl, heterocyclic, haloalkyl, arylalkylamino, alkylaminoalkyl, dialkylaminoalkyl, alkyl, alkenyl, alkynyl, heteroarylalkyl, and heterocyclicalkyl;

R^9 is independently selected from the group consisting of: hydrido, lower alkyl, aryl, heteroaryl, arylalkyl, heterocyclic, cycloalkyl, heterocyclicalkyl, haloalkyl, arylalkylamino, amino, aminoalkyl, aminoacyl, nitro, azido, and heteroarylalkyl, wherein alkyl, aryl, heteroaryl, aminoalkyl, or arylalkyl are

optionally substituted with one or more radical selected from the group consisting of: alkylsulfonamide, sulfamyl, alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, aminoalkyl, alkylaminoalkyl, alkoxy, halogen, acyloxy, oxy, formyl, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, nitro, azido, benzyloxy, dialkylaminoacyl, thioalkyl, aminoacyloxy, thiocyanate, isothiocyanate, alkyldioxy, hydroxyalkyl, alkylamino, alkyloxycarbonyl, alkoxyalkyl, alkenylamino, alkynylamino, alkenyl, alkynyl, dialkylaminoalkyloxy, and heterocyclic optionally substituted with alkyl, alkylamino, aminoalkyl, hydroxyalkyl, and alkylaminoalkyl;

$\mathbf{R^{10}}$ is independently selected from the group consisting of: hydrido, lower alkyl, heteroaryl, heterocyclic, haloalkyl, arylalkylamino, heteroarylalkyl, aryl, and arylalkyl, wherein aryl, heteroaryl, heterocyclic, or arylalkyl are optionally substituted with one or more radical selected from alkyl, alkoxy, halogen, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, benzyloxy, dialkylaminoalkyloxy, and heterocyclic,

$\mathbf{R^{10'}}$ is independently selected from the group consisting of: hydrido, lower alkyl, heteroaryl, heterocyclic, haloalkyl, arylalkylamino, heteroarylalkyl, aryl, and arylalkyl, wherein aryl, heteroaryl, heterocyclic, or arylalkyl are optionally substituted with one or more radical selected from alkyl, alkoxy, halogen, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, benzyloxy, dialkylaminoalkyloxy, and heterocyclic,

$\mathbf{R^{11}}$ is selected from the group consisting of: hydrido, halogen, haloalkyl, CN, CO_2R^5, lower alkyl, lower alkenyl, lower alkynyl, alkoxy, and $CONH_2$;

$\mathbf{R^{12}}$ is selected from the group consisting of: hydrido, halogen, alkyl, and alkoxy;

$\mathbf{R^{13}}$ is selected from the group consisting of: hydrido, alkyl, aryl, arylalkyl, heteroaryl, heterocyclicalkyl, and heteroarylalkyl, wherein aryl, alkyl, arylalkyl, heteroaryl, heterocyclicalkyl, or heteroarylalkyl are optionally

substituted with one or more radicals selected from the group consisting of: OR^{14}, $N(R^{14})R^{14'}$, and glycols;

R^{14} is independently selected from the group consisting of: hydrido, and lower alkyl;

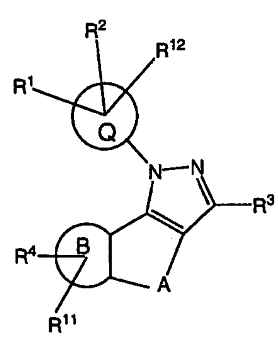
$R^{14'}$ is independently selected from the group consisting of: hydrido, and lower alkyl;

R^{15} is selected from the group consisting of: hydrido, halogen, alkyl, cycloalkyl, aryl, haloalkyl, heteroaryl, heterocyclic, alkylalkene, alkylalkyne, hydroxy, hydroxyalkyl, alkylhydroxy, amino, aminoalkyl, alkylamino, alkylaminoalkyl, alkylhydroxyalkyl, nitro, cyano, alkylthio, alkylsulfinyl, and alkylsulfonyl; wherein aryl or arylalkyl are optionally substituted with one or more radical selected from alkyl, alkoxy, halo, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, benzyloxy, dialkylaminoalkyloxy, heterocyclic; and

R^{16} is independently selected from the group consisting of: hydrido, aryl, arylalkyl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkoxy, and alkoxyalkyl;

or isomers, tautomers, carriers, esters, prodrugs, pharmaceutically acceptable salts thereof.

[0019] A preferred class of compounds is defined by formula III



wherein

A is $(CH_2)_m$, wherein each CH_2 may be independently substituted with one or more substitution selected from the group consisting of: hydroxy, halo, alkoxy, lower alkyl, amino, aminoalkyl, alkylamino, alkenyl, and alkynyl;

m is 0 to 8;

Q is a 5 or 6 membered heteroaryl, or aryl, optionally saturated, or optionally substituted with R^1, R^2, or R^{12};

B is an aromatic heterocyclic;

$\mathbf{R^1}$ is selected from the group consisting of: hydrido, halogen, alkyl, aryl, heteroaryl, alkenyl, alkynyl, haloalkyl, CN, NO_2, OR^5, $OCOOR^5$, CO_2R^7, $CON(R^6)R^7$, COR^6, SR^6, SOR^6, SO_2R^6, NR^6R^7, NR^6COR^7, NR^6CONHR^7, $NR^6SO_2R^7$, $NR^6SO_2NHR^7$, and $SO_2N(R^6)R^7$ wherein R^6 and R^7 may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from the group consisting of: S, SO, SO_2, O, and NR^6; wherein said alkenyl, alkynyl, alkyl, aryl, heteroaryl or OR^5 are optional substituted with, hydrido, halogen, alkyl, hydroxyalkyl, aryl, heteroaryl, haloalkyl, $COCF_3$, CN, NO_2, OR^5, $OCOOR^5$, CO_2R^7, $CON(R^6)R^7$, COR^6, SR^6, SOR^6, SO_2R^6, NR^6R^7, NR^6COR^7, NR^6CONHR^7, $NR^6SO_2R^7$, $NR^6SO_2NHR^7$, and $SO_2N(R^6)R^7$ wherein R^6 and R^7 may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from the group consisting of: S, SO, SO_2, O, and NR^6;

$\mathbf{R^2}$ is selected from the group consisting of: halogen, hydrido, hydroxyalkyl, alkyl, OR^6, CN, NO_2, SR^6, NHR^6, $CON(R^6)R^7$, $NHCONHR^6$, CO_2H, and haloalkyl;

$\mathbf{R^1}$ and $\mathbf{R^2}$ may be taken together to form a 5 to 7 membered saturated or unsaturated carbocyclic ring optionally containing 0 to 3 heteroatoms selected from the group consisting of: N, O, or S, and wherein said ring is optionally substituted with R^1;

$\mathbf{R^3}$ is $CONHR^{16}$;

$\mathbf{R^4}$ is selected from the group consisting of: halogen, alkylsulfinyl, alkylsulfonyl, cyano, alkoxycarbonyl, alkyl, haloalkyl, hydrido, hydroxyalkyl, haloalkoxy, heterocyclic, nitro, acylamino, aryl, heteroaryl,

and alkenyl, OR^{13}, SR^8, $SO_2N(R^8)R^{8'}$, NHR^9, $NHCOR^9$, NR^9COR^9, $NHCO(OR^9)$, $NR^9CO(OR^9)$, $NR^8SO_2R^{10}$, $NHSO_2N(R^{10})R^{10'}$, $NR^6CON(R^{10})R^{10'}$, COR^9, CO_2R^8, $CON(R^8)R^{8'}$, wherein R^8 and $R^{8'}$ may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from S, SO, SO_2, O, N, and NR^6, and wherein R^{10} and $R^{10'}$ may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from S, SO, SO_2, O, N, and NR^6 wherein said aryl, heterocyclic, heteroaryl, or alkenyl are optionally substituted with R^9;

R^5 is selected from the group consisting of: hydrido, alkyl, aryl, arylalkyl, heteroaryl, heterocyclicalkyl, and heteroarylalkyl, wherein aryl, alkyl, arylalkyl, heteroaryl, heterocyclicalkyl, or heteroarylalkyl are optionally substituted with one or more radicals selected from the group consisting of: OR^{14}, $N(R^{14})R^{14'}$, and glycols;

R^6 is independently selected from the group consisting of: hydrido, aryl, heteroaryl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, heterocyclicalkyl, and heterocyclic;

R^7 is independently selected from the group consisting of: hydrido, aryl, heteroaryl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, heterocyclicalkyl, and heterocyclic;

R^8 is independently selected from the group consisting of: hydrido, aryl, heteroaryl, arylalkyl, heterocyclic, haloalkyl, arylalkylamino, alkylaminoalkyl, dialkylaminoalkyl, alkyl, alkenyl, alkynyl, heteroarylalkyl, and heterocyclicalkyl;

$R^{8'}$ is independently selected from the group consisting of: hydrido, aryl, heteroaryl, arylalkyl, heterocyclic, haloalkyl, arylalkylamino, alkylaminoalkyl, dialkylaminoalkyl, alkyl, alkenyl, alkynyl, heteroarylalkyl, and heterocyclicalkyl;

R^9 is independently selected from the group consisting of: hydrido, lower alkyl, aryl, heteroaryl, arylalkyl, heterocyclic, cycloalkyl, heterocyclicalkyl,

haloalkyl, arylalkylamino, amino, aminoalkyl, aminoacyl, nitro, azido, and heteroarylalkyl, wherein alkyl, aryl, heteroaryl, aminoalkyl, or arylalkyl are optionally substituted with one or more radical selected from the group consisting of: alkylsulfonamide, sulfamyl, alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, aminoalkyl, alkylaminoalkyl, alkoxy, halogen, acyloxy, oxy, formyl, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, nitro, azido, benzyloxy, dialkylaminoacyl, thioalkyl, aminoacyloxy, thiocyanate, isothiocyanate, alkyldioxy, hydroxyalkyl, alkylamino, alkyloxycarbonyl, alkoxyalkyl, alkenylamino, alkynylamino, alkenyl, alkynyl, dialkylaminoalkyloxy, and heterocyclic optionally substituted with alkyl, alkylamino, aminoalkyl, hydroxyalkyl, and alkylaminoalkyl;

R^{10} is independently selected from the group consisting of: hydrido, lower alkyl, heteroaryl, heterocyclic, haloalkyl, arylalkylamino, heteroarylalkyl, aryl, and arylalkyl, wherein aryl, heteroaryl, heterocyclic, or arylalkyl are optionally substituted with one or more radical selected from alkyl, alkoxy, halogen, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, benzyloxy, dialkylaminoalkyloxy, and heterocyclic,

$R^{10'}$ is independently selected from the group consisting of: hydrido, lower alkyl, heteroaryl, heterocyclic, haloalkyl, arylalkylamino, heteroarylalkyl, aryl, and arylalkyl, wherein aryl, heteroaryl, heterocyclic, or arylalkyl are optionally substituted with one or more radical selected from alkyl, alkoxy, halogen, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, benzyloxy, dialkylaminoalkyloxy, and heterocyclic,

R^{11} is selected from the group consisting of: hydrido, halogen, haloalkyl, CN, CO_2R^5, lower alkyl, lower alkenyl, lower alkynyl, alkoxy, and $CONH_2$;

R^{12} is selected from the group consisting of: hydrido, halogen, alkyl, and alkoxy;

R^{13} is selected from the group consisting of: hydrido, alkyl, aryl, arylalkyl, heteroaryl, heterocyclicalkyl, and heteroarylalkyl, wherein aryl, alkyl,

arylalkyl, heteroaryl, heterocyclicalkyl, or heteroarylalkyl are optionally substituted with one or more radicals selected from the group consisting of: OR^{14}, $N(R^{14})R^{14'}$, and glycols;

R^{14} is independently selected from the group consisting of: hydrido, and lower alkyl;

$R^{14'}$ is independently selected from the group consisting of: hydrido, and lower alkyl;

R^{15} is selected from the group consisting of: hydrido, halogen, alkyl, cycloalkyl, aryl, haloalkyl, heteroaryl, heterocyclic, alkylalkene, alkylalkyne, hydroxy, hydroxyalkyl, alkylhydroxy, amino, aminoalkyl, alkylamino, alkylaminoalkyl, alkylhydroxyalkyl, nitro, cyano, alkylthio, alkylsulfinyl, and alkylsulfonyl; wherein aryl or arylalkyl are optionally substituted with one or more radical selected from alkyl, alkoxy, halo, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, benzyloxy, dialkylaminoalkyloxy, heterocyclic; and

R^{16} is independently selected from the group consisting of: hydrido, aryl, arylalkyl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkoxy, and alkoxyalkyl;

or isomers, tautomers, carriers, esters, prodrugs, pharmaceutically acceptable salts thereof.

Definitions

[0020] The present invention includes the use of all hydrates, solvates, complexes and prodrugs of the compounds of this invention. Prodrugs are any covalently bonded compounds, which release the active parent drug according to Formula I in vivo. If a chiral center or another form of an isomeric center is present in a compound of the present invention all forms of such isomer or isomers, including enantiomers and diastereomers, are intended to be covered herein. Compounds containing a chiral center may be used as a racemic mixture, an enantiomerically enriched mixture, or the racemic mixture may be separated using

well-known techniques and an individual enantiomer may be used alone. In cases in which compounds have unsaturated carbon-carbon double bonds, both the cis (Z) and trans (E) isomers are within the scope of this invention. In cases wherein compounds may exist in tautomeric forms, such as keto-enol tautomers, each tautomeric form is contemplated as being included within this invention whether existing in equilibrium or predominantly in one form.

[0021] The meaning of any substituent at any one occurrence in Formula I or any sub-formula thereof is independent of its meaning, or any other substituents meaning, at any other occurrence, unless specified otherwise.

[0022] The present invention includes the use of all hydrates, solvates, complexes and prodrugs of the compounds of this invention. Prodrugs are any covalently bonded compounds, which releases the active parent drug according to Formula I or Formula II in vivo. If a chiral center or another form of an isomeric center is present in a compound of the present invention all forms of such isomer or isomers, including enantiomers and diastereomers, are intended to be covered herein. Compounds containing a chiral center may be used as a racemic mixture, an enantiomerically enriched mixture, or the racemic mixture may be separated using well-known techniques and an individual enantiomer may be used alone. In cases in which compounds have unsaturated carbon-carbon double bonds, both the cis (Z) and trans (E) isomers are within the scope of this invention. In cases wherein compounds may exist in tautomeric forms, such as keto-enol tautomers, each tautomeric form is contemplated as being included within this invention whether existing in equilibrium or predominantly in one form.

[0023] The meaning of any substituent at any one occurrence in Formula I or Formula II or any sub-formula thereof is independent of its meaning, or any other substituents meaning, at any other occurrence, unless specified otherwise.

[0024] The term "alkyl" is used, either alone or within other terms such as "haloalkyl" and "alkylsulfonyl"; it embraces linear or branched radicals having one

to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about five carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, hexyl, octyl and the, like. The term "hydrido" denotes a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical or two hydrido radicals may be attached to a carbon atom to form a methylene ($-CH_2-$) radical. The term "halo" means halogens such as fluorine, chlorine, and bromine or iodine atoms. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl, and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have a bromo, chloro, or a fluoro atom within the radical. Dihalo radicals may have two or more of the same halo atoms or a combination of different halo radicals and polyhaloalkyl radicals may have more than two of the same halo atoms or a combination of different halo radicals. The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxylradicals. The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms, such as methoxy radical. The term "alkoxyalkyl" also embraces alkyl radicals having two or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. The "alkoxy" or "alkoxyalkyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro, or bromo, to provide "haloalkoxy" or "haloalkoxyalkyl" radicals. Examples of "alkoxy" radicals include methoxy, butoxy, and trifluoromethoxy. The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two, or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronapthyl, indane, and biphenyl. The term "heterocyclic" embraces saturated, partially saturated, and unsaturated heteroatom-containing ring-shaped radicals, where the heteroatoms may be selected from nitrogen, sulfur and

oxygen. Examples of saturated heterocyclic radicals include pyrrolidyl and morpholinyl. The term "heteroaryl" embraces unsaturated heterocyclic radicals. Examples of unsaturated heterocyclic radicals, also termed "heteroaryl" radicals include thienyl, pyrrolyl, furyl, pyridyl, pyrimidyl, pyrazinyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, thiazolyl, and tetrazolyl. The term also embraces radicals where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like. The term "heterocyclic alkyl" embraces alkyl attached to the heterocyclic. The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals $-SO_2-$. "Alkylsulfonyl", embraces alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. The term "arylsulfonyl" embraces sulfonyl radicals substituted with an aryl radical. The terms "sulfamyl" or "sulfonamidyl", whether alone or used with terms such as "N-alkylsulfamyl", "N-arylsulfamyl", "N,N-dialkylsulfamyl" and "N-alkyl-N-arylsulfamyl", denotes a sulfonyl radical substituted with an amine radical, forming a sulfonamide ($-SO_2-NH_2$). The terms "N-alkylsulfamyl" and "N,N-dialkylsulfamyl" denote sulfamyl radicals substituted, respectively, with one alkyl radical, a cycloalkyl ring, or two alkyl radicals. The terms "N-arylsulfamyl" and "N-alkyl-N-arylsulfamyl" denote sulfamyl radicals substituted, respectively, with one aryl radical, and one alkyl and one aryl radical. The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes $-CO_2H$. The term "carboxyalkyl" embraces radicals having a carboxyradical as defined above, attached to an alkyl radical. The term "carbonyl", whether used alone or with other terms, such as "alkylcarbonyl", denotes $-(C{=}O)-$. The term "alkylcarbonyl" embraces radicals having a carbonyl radical substituted with an alkyl radical. An example of an "alkylcarbonyl" radical is $CH_3-(C{=}O)-$. The term "alkylcarbonylalkyl" denotes an alkyl radical substituted with an "alkylcarbonyl" radical. The term "alkoxycarbonyl" means a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl (C=O) radical. Examples of such "alkoxycarbonyl" radicals include $(CH_3)_3CO-C{=}O)-$ and $-(O{=})C-OCH_3$. The term "alkoxycarbonylalkyl" embraces radicals having "alkoxycarbonyl", as defined above substituted to an alkyl radical. Examples of such

"alkoxycarbonylalkyl" radicals include $(CH_3)_3COC(=O)(CH_2)_2$– and –$(CH_2)_2(O=)COCH_3$. The term "amido" when used by itself or with other terms such as "amidoalkyl", "N-monoalkylamido", "N-monoarylamido", "N,N-dialkylamido", "N-alkyl-N-arylamido", "N-alkyl-N-hydroxyamido" and "N-alkyl-N-hydroxyamidoalkyl", embraces a carbonyl radical substituted with an amino radical. The terms "N-alkylamido" and "N,N-dialkylamido" denote amido groups which have been substituted with one alkyl radical and with two alkyl radicals, respectively. The terms "N-monoarylamido" and "N-alkyl-N-arylamido" denote amido radicals substituted, respectively, with one aryl radical, and one alkyl and one aryl radical. The term "N-alkyl-N-hydroxyamido" embraces amido radicals substituted with a hydroxyl radical and with an alkyl radical. The term "N-alkyl-N-hydroxyamidoalkyl" embraces alkyl radicals substituted with an N-alkyl-N-hydroxyamido radical. The term "amidoalkyl" embraces alkyl radicals substituted with amido radicals. The term "aminoalkyl" embraces alkyl radicals substituted with amino radicals. The term "alkylaminoalkyl" embraces aminoalkyl radicals having the nitrogen atom substituted with an alkyl radical. The term "amidino" denotes an –C(=NH)–NH_2 radical. The term "cyanoamidino" denotes an –C(=N–CN)–NH_2 radical. The term "heterocycloalkyl" embraces heterocyclic-substituted alkyl radicals such as pyridylmethyl and thienylmethyl. The term "aralkyl" embraces aryl-substituted alkyl radicals such as benzyl, diphenylmethyl, triphenylmethyl, phenethyl, and diphenethyl. The terms benzyl and phenylmethyl are interchangeable. The term "cycloalkyl" embraces radicals having three to ten carbon atoms, such as cyclopropyl cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. The term "cycloalkenyl" embraces unsaturated radicals having three to ten carbon atoms, such as cylopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, and cycloheptenyl. The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. An example of "alkylthio" is methylthio, (CH_3–S–). The term "alkylsulfinyl" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent –S(=O)– atom. The terms "N-alkylamino" and "N, N-dialkylamino" denote amino groups which have been substituted with one alkyl radical and with two alkyl radicals, respectively. The term "acyl", whether used

alone, or within a term such as "acylamino", denotes a radical provided by the residue after removal of hydroxyl from an organic acid. The term "acylamino" embraces an amino radical substituted with an acyl group. An example of an "acylamino" radical is acetylamino ($CH_3C(=O)–NH–$).

[0025] Another aspect of the present invention is chemical intermediates in the synthesis of the claimed compounds.

[0026] Another aspect of the present invention is methods of syntheses of the claimed compounds.

[0027] Compounds of Formula I or Formula II would be useful for, but not limited to, the treatment of inflammation in a subject, and for treatment of other inflammation-associated disorders, such as, as an analgesic in the treatment of pain and headaches, or as an antipyretic for the treatment of fever. For example, compounds of Formula I or Formula II would be useful to treat arthritis, including but not limited to rheumatoid arthritis, spondylo arthopathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus, and juvenile arthritis. Such compounds of Formula I or Formula II would be useful in the treatment of asthma, bronchitis, menstrual cramps, tendinitis, bursitis, and skin related conditions such as psoriasis, eczema, burns, and dermatitis. Compounds of Formula I or Formula II also would be useful to treat gastrointestinal conditions such as inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome, and ulcerative colitis and for the prevention of colorectal cancer. Compounds of Formula I or Formula II would be useful in treating inflammation in such diseases as vascular diseases such as vascularitus, migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, myasthenia gravis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, hypersensitivity, conjunctivitis, swelling occurring after injury, myocardial ischemia, and the like. The compounds of the present invention may also be used for pain. The compounds are useful as antiinflammatory agents, such as for the treatment of arthritis, with the additional benefit of having

significantly less harmful side effects. The compounds of formula I or II are useful as agents for treating cancer or anticancer agents. The compounds of formula I or II may be proapoptotic, antiapoptotic, anticell cycle progressive, antiinvasive, antiproliferative, antiangiogenic, and antimetastatic. The cancer may be colon, ovarian, breast, prostate, gastric, B-cell lymphoma, and multiple myeloma. More specifically, the compounds of this invention are useful in the treatment of a variety of cancers including, but not limited to: carcinoma such as bladder, breast, colon, kidney, liver, lung, including small cell lung cancer, esophagus, gall-bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, including squamous cell carcinoma; hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkett's lymphoma; hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia; tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma; tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma and schwannomas; other tumors, including melanoma, seminoma, teratocarcinoma, osteosarcoma, xeroderma pigmentosum, keratoxanthoma, thyroid follicular cancer and Kaposi's sarcoma. Due to the key role of protein kinases in the regulation of cellular proliferation, these compounds are also useful in the treatment of a variety of cell proliferative disorders such as, for instance, benign prostate hyperplasia, familial adenomatosis, polyposis, neuro-fibromatosis, psoriasis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis glomerulonephritis and post-surgical stenosis and restenosis. The compounds of formula I or II may be used as an anitviral agent. The compounds of this invention are useful as inhibitors of protein kinases. The compounds of this invention are useful as inhibitors of IKK1 and/or IKK2, IKKα/IKKβ heterodimer, TBK or IKK*i*. The compounds of the invention may also useful as inhibitors of other protein kinases such as, for instance, protein kinase C in different isoforms, cyclin dependent kinase (cdk), Met, PAK-4, PAK-5, ZC-1, STLK-2, DDR-2, Aurora 1, Aurora 2, Bub-1, PLK, Chk1, Chk2, HER2, raf1, MEK1, MAPK, EGF-R, PDGF-R, FGF-R, IGF-R, VEGF-R, PI3K, weel kinase,

Src, Abl, Akt, ILK, MK-2, Cdc7, Nek, and thus be effective in the treatment of diseases associated with other protein kinases. The present invention preferably includes compounds, which selectively inhibit IKK2 over other kinases. Preferably the compounds have a selectivity ratio of IKK2 inhibition over other kinase inhibition of at least 50, and more preferably of at least 100. The present invention preferably includes compounds, which selectively inhibit IKK2 over IKK1. Preferably, the compounds have an IKK2 IC50 of less than 1 μM, and have a selectivity ratio of IKK2 inhibition over IKK1 inhibition of at least 50, and more preferably of at least 100. Even more preferably, the compounds have an IKK1 IC50 of greater than 10 μM, and more preferably of greater than 100 μM. The compounds of formula may also be used to treat angiogenesis associated cardiovascular, ophthalmology and osteoporosis disorders. The compounds of the present invention may also be used for treatment of knee injury such as sport injuries.

[0028] While it is possible for an active ingredient to be administered alone as the raw chemical, it is preferable to present it as a pharmaceutical formulation. The present invention comprises a pharmaceutical composition comprising a therapeutically effective amount of a compound of the present invention in association with at least one pharmaceutically acceptable carrier, adjuvant, or diluent. The present invention also comprises a method of treating inflammation or inflammation associated disorders in a subject, the method comprising administering to the subject having such inflammation or disorders a therapeutically effective amount of a compound of the present invention. Also included in the family of compounds of the present invention are the pharmaceutically acceptable salts thereof. The term "pharmaceutically acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically acceptable. Suitable pharmaceutically acceptable acid addition salts of compounds of the present invention may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric, and phosphoric acid. Appropriate organic acids may be

selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicyclic, salicyclic, phydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, stearic, cyclohexylaminosulfonic, algenic, β-hydroxybutyric, salicyclic, galactaric and galacturonic acid. Suitable pharmaceutically acceptable base addition salts of compounds of the present invention include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methyl-glucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compound of the present invention by reacting, for example, the appropriate acid or base with the compound of the present invention.

[0029] Also embraced within this invention are pharmaceutical compositions comprising one or more compounds of the present invention in association with one or more non-toxic, pharmaceutically acceptable carriers and/or diluents and/or adjuvants and/or excipient (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. Accordingly, the compounds of the present invention may be used in the manufacture of a medicament. Pharmaceutical compositions of the compounds of the present invention prepared as herein before described may be formulated as solutions or lyophilized powders for parenteral administration. Powders may be reconstituted by addition of a suitable diluent or other pharmaceutically acceptable carrier prior to use. The liquid formulation may be a buffered, isotonic aqueous solution. The compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The compounds and composition may, for example, be administered intravascularly, intraperitoneally, intravenously, subcutaneously,

intramuscularly, intramedullary, orally, or topically. For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension, or liquid. The active ingredient may also be administered by injection as a composition wherein, for example, normal isotonic saline solution, standard 5% dextrose in water or buffered sodium or ammonium acetate solution may be used as a suitable carrier. Such formulation is especially suitable for parenteral administration, but may also be used for oral administration or contained in a metered dose inhaler or nebulizer for insufflation. It may be desirable to add excipients such as polyvinylpyrrolidone, gelatin, hydroxy cellulose, acacia, polyethylene glycol, mannitol, sodium chloride, or sodium citrate. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. The amount of therapeutically active compound that is administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the disease, the route and frequency of administration, and the particular compound employed, and thus may vary widely. The pharmaceutical compositions may contain active ingredient in the range of about 0.1 to 2000 mg, preferably in the range of about 0.5 to 500 mg and most preferably between about 1 and 100 mg. A daily dose of about 0.01 to 100 mg/kg bodyweight, preferably between about 0.1 and about 50 mg/kg body weight and most preferably between about 1 to 20 mg/kg bodyweight, may be appropriate. The daily dose can be administered in one to four doses per day. For therapeutic purposes, the compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered orally, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled release formulation as may be provided in a dispersion of active compound in a

sustained release material such as glyceryl monostearate, glyceryl distearate, hydroxypropylmethyl cellulose alone or with a wax. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. The pharmaceutical preparations are made following the conventional techniques of pharmacy involving milling, mixing, granulating, and compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion, or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered orally or filled into a soft gelatin capsule. For rectal administration, the compounds of the present invention may also be combined with excipients such as cocoa butter, glycerin, gelatin, or polyethylene glycols and molded into a suppository. The methods of the present invention include topical administration of the compounds of the present invention. By topical administration is meant non-systemic administration, including the application of a compound of the invention externally to the epidermis, to the buccal cavity and instillation of such a compound into the ear, eye, and nose, wherein the compound does not significantly enter the blood stream. By systemic administration is meant oral, intravenous, intraperitoneal, and intramuscular administration. The amount of a compound of the present invention (hereinafter referred to as the active ingredient) required for therapeutic or prophylactic effect upon topical administration will, of course, vary with the compound chosen, the nature and severity of the condition being treated and the animal undergoing treatment, and is ultimately at the discretion of the physician.

[0030] The topical formulations of the present invention, both for veterinary and for human medical use, comprise an active ingredient together with one or more acceptable carriers therefore, and optionally any other therapeutic ingredients. The

carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of where treatment is required such as: liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose. The active ingredient may comprise, for topical administration, from 0.01 to 5.0 wt%. of the formulation.

[0031] Drops according to the present invention may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container, which is then sealed and sterilized by autoclaving, or maintaining at 90-100° C for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.00217c), benzalkonium chloride (0.0 1%) and chlorhexidine acetate (0.0 1%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol, and propylene glycol.

[0032] Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil. Creams, ointments, or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy basis. The basis may comprise

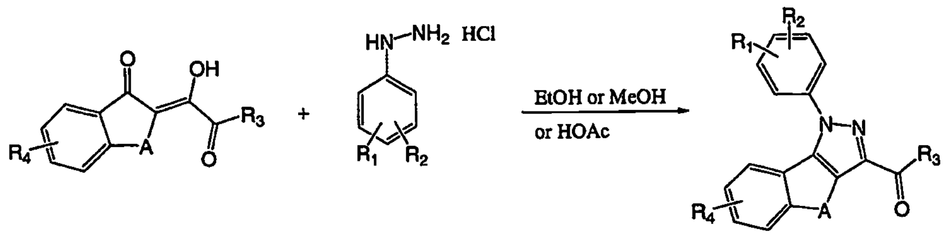
hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives, or a fatty acid such as stearic or oleic acid together with an alcohol such as propylene glycol or macrogols. The formulation may incorporate any suitable surface-active agent such as an anionic, cationic, or non-ionic surface-active agent such as sorbitan esters or polyoxyethylene derivatives thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as silicaceous silicas, and other ingredients such as lanolin may also be included. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art. Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations.

GENERAL SYNTHETIC PROCEDURES

[0033] The starting materials used herein are commercially available or are prepared by routine methods well known to those of ordinary skill in the art and can be found in standard reference books, such as the COMPENDIUM OF ORGANIC SYNTHETIC METHODS, Vol. I-VI (published by Wiley-Interscience).

[0034] The compounds of the invention can be synthesized according to the following procedures of Schemes I-XVI, wherein the R1-R7 substituents, linker A, are as defined for Formula I and Formula II, above, except where further noted.

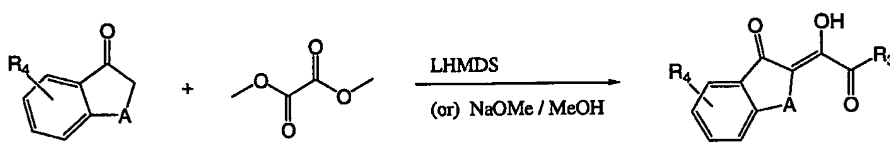
SCHEME I



1 2 3

[0035] Synthetic Scheme I illustrates the procedure used to prepare the anti-inflammatory pyrazoles of the present invention. 1,3-Dicarbonyl compounds such as **1**, or the shown enol form which is in equilibrium with the 1,3-diketone, are allowed to react with a substituted hydrazine hydrochloride **2** in warm methanol or ethanol or acetic acid to provide the pyrazoles **3** via a condensation reaction.

SCHEME II

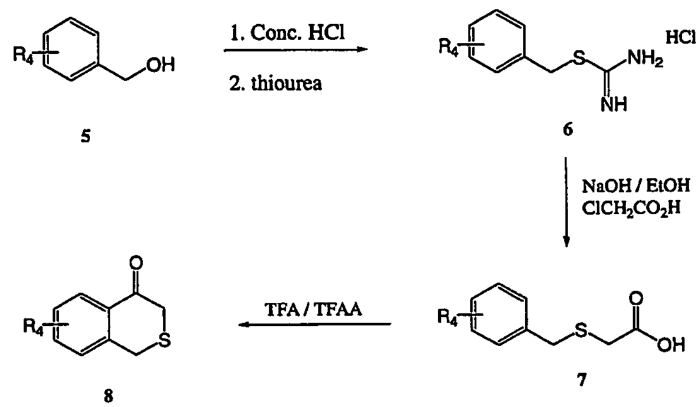


4 1

[0036] Synthetic Scheme II illustrates the procedure for the preparation of substituted diketones **1**. An appropriately substituted ketone, including but not limited to; indanones, 3-coumaranones, 3-thiocourmaranones, 3-azacourmaranones, 1-tetralones, chromanones, thiochromanones, azachromanones, isochromanones, isothiochromanones, isoazachromanones, **4** is first treated with base, such as sodium methoxide, lithium bistrimethylsilylamide or lithium diisopropylamide (LDA), followed by condensation with a suitable acylating agent, such as; dimethyl or diethyl oxalate, in an appropriate solvent, such as methanol, diethyl ether or tetrahydrofuran, to provide 1,3-dicarbonyl compounds **1** which are suitable for conversion into anti-inflammatory pyrazoles as illustrated in Scheme 1.

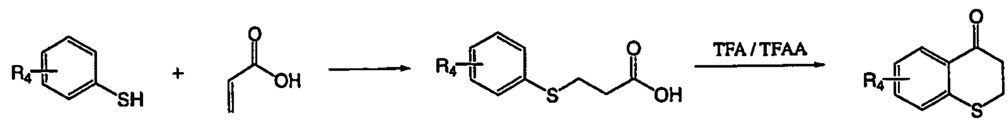
Alternatively, the dicarbonyl compounds **1** can be directly prepared from commercially available cyclic ketones **4**.

SCHEME III



[0037] Synthetic Scheme III illustrates the three step procedure for the preparation of substituted isothiochromanones. In step one, an appropriately substituted benzyl alcohol **5** is converted into the corresponding benzyl chloride by stirring with concentrated hydrochloric acid and then immediately converted into a thiouronium salt 6 upon treatment with thiourea at reflux. In step two, the thiouronium salt is converted to the free mercaptide, according to the procedure of Lumma and Berchtold *(J. Org. Chem.*, 34, 1566 (1969), and then trapped with chloroacetic acid or a related salt to provide the acetic acid derivatives **7**. In step three, the acids **7** are reacted with trifluoroacetic anhydride (TFAA) in trifluoroacetic acid (TFA) to give the isothiochromanone products **8**. The thiouronium salts **6** can also be prepared from appropriate commercially available benzyl halides.

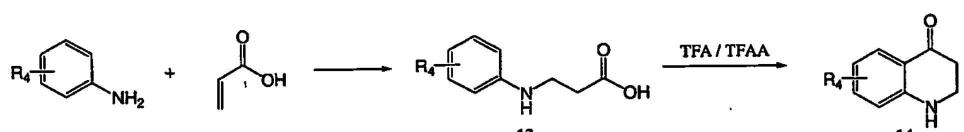
SCHEME IV



9 10 11

[0038] Synthetic Scheme IV illustrates a three step procedure used for the preparation of substituted thiochromanones. In step one, an appropriate substituted thiophenol **9** is converted into the corresponding propionic acid derivatives **10** upon treatment with acrylic acid at a temperature in a range of room temperature to about 50°C. In step two, the propionic acids **10** are subjected to treatment with a mixture of trifluoroacetic anhydride and trifluoroacetic acid to effect intramolecular Friedel-Crafts acylation, thus providing thiochromanones **11**. Alternatively, the Friedel-Crafts acylation can be affected with H_2SO_4. Dicarbonyl compounds 1 can also be directly prepared from commercially available thiochromanones **11**.

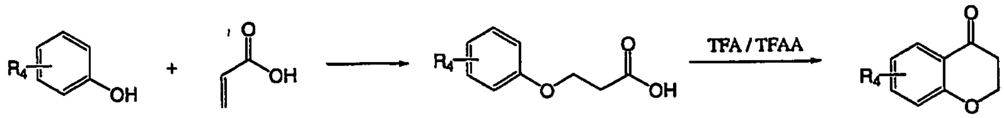
SCHEME V



12 13 14

[0039] Synthetic Scheme V illustrates a three step procedure used for the preparation of substituted azachromanones. In step one, an appropriate substituted aniline **12** is converted into the corresponding propionic acid derivatives **13** upon treatment with acrylic acid at a temperature in a range of room temperature to about 50°C. In step two, the propionic acids **13** are subjected to treatment with a mixture of H_2SO_4 to effect intramolecular Friedel-Crafts acylation, thus providing azachromanones **14**. Dicarbonyl compounds 1 can also be directly prepared from commercially available azachromanones **14**. Suitable protection of the aza nitrogen is effected when necessary using protecting groups such as benzyl, benzoyl, benzyloxycarbonyl (Cbz), t-butoxycarbonyl (Boc) or sulfonamido groups (mesyl, Ms or tosyl, Ts).

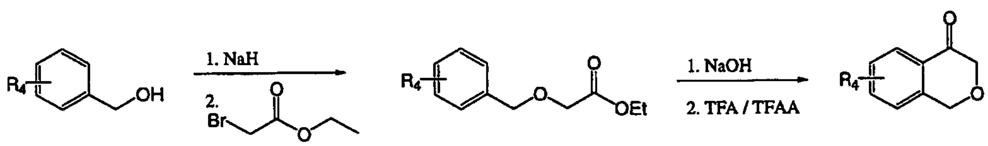
SCHEME VI



15 16 17

[0040] Synthetic Scheme VI details the three step procedure used to prepare substituted chromanone derivatives **17**. In step one, substituted phenols **15** are condensed with acrylic acid to afford 3-phenoxypropionic acids **16**. In step two, the acids **16** are treated with a mixture of trifluoroacetic anhydride, and trifluoroacetic acid to affect intramolecular Friedel-Crafts acylation affording selected chromanones **17**. Alternatively, the Friedel-Crafts acylation can be affected with H_2SO_4. The dicarbonyl compounds **1** can be directly formed from commercially available chromanones **17**.

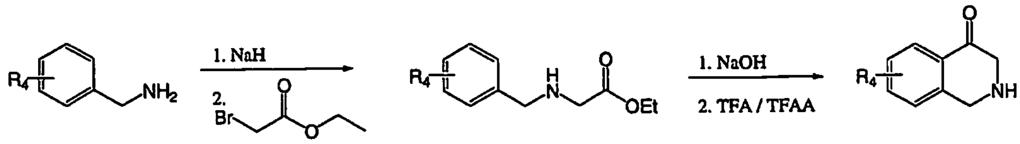
SCHEME VII



5 18 19

[0041] Synthetic Scheme VII illustrates a procedure used to prepare isochromanone derivatives **19**. In step one, selected benzyl alcohol derivatives **5** are treated with sodium hydride or other suitable base and subsequently treated with ethyl bromoacetate to provide the desired ethers **18**. In step two, the ester group of **18** is hydrolyzed with aqueous sodium hydroxide and then treated with a mixture of trifluoroacetic acid and trifluoroacetic anhydride to promote intramolecular Friedel-Crafts acylation affording isochromanone **19** derivatives.

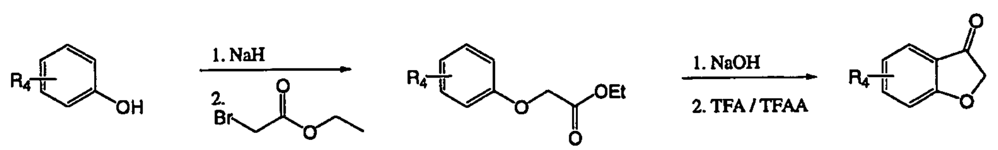
SCHEME VIII



20 21 22

[0042] Synthetic Scheme VII illustrates a procedure used to prepare isoazachromanone derivatives **22**. In step one, selected benzyl amine derivatives **20** are treated with ethyl bromoacetate and a suitable acid scavenger, such as triethylamine, to provide the desired amines **21**. In step two, the ester group of **21** is hydrolyzed with aqueous sodium hydroxide and then treated with a mixture of trifluoroacetic acid and trifluoroacetic anhydride to promote intramolecular Friedel-Crafts acylation affording isochromanone **22** derivatives. Suitable protection of the aza nitrogen is effected when necessary using protecting groups such as benzyl, benzoyl, benzyloxycarbonyl (Cbz), t-butoxycarbonyl (Boc) or sulfonamido groups (mesyl, Ms or tosyl, Ts).

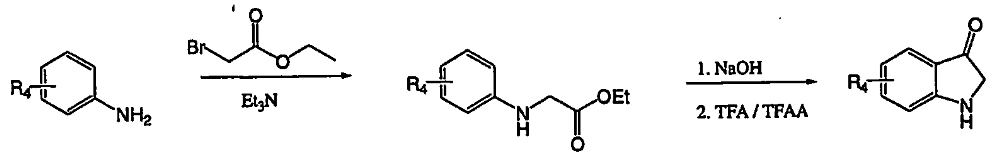
SCHEME IX



15 23 24

[0043] Synthetic Scheme IX illustrates a procedure used to prepare substituted 3-coumaranones **24**. Phenols **15** are first treated with a base, such as NaOH, lithium diisopropyl amide (LDA) or sodium methoxide followed by condensation with ethyl bromoacetate in an appropriate solvent such as diethyl ether, ethanol, or tetrahydrofuran to provide the phenoxyacetate **23**. In step two, the ester group of **23** is hydrolyzed with aqueous sodium hydroxide and then treated with a mixture of trifluoroacetic acid and trifluoroacetic anhydride to promote intramolecular Friedel-Crafts acylation affording 3-coumaranones derivatives **24**.

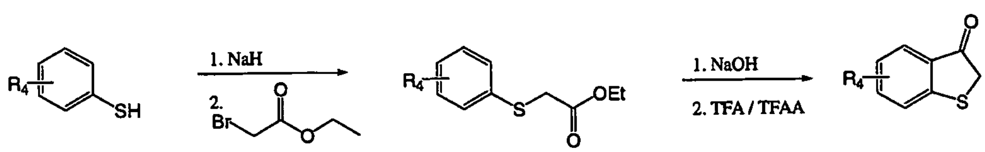
SCHEME X



12 25 26

[0044] Synthetic Scheme X illustrates a procedure used to prepare substituted 3-azacoumaranones **26**. Anilines **12** are treated with a acid scavenger, such as triethylamine followed by alkylation with ethyl bromoacetate in an appropriate solvent such as diethyl ether, ethanol, or tetrahydrofuran to provide the phenoxyacetate **25**. In step two, the ester group of **25** is hydrolyzed with aqueous sodium hydroxide and then treated with a mixture of trifluoroacetic acid and trifluoroacetic anhydride to promote intramolecular Friedel-Crafts acylation affording 3-azacoumaranones derivatives **24**. Suitable protection of the aza nitrogen is effected when necessary using protecting groups such as benzyl, benzoyl, benzyloxycarbonyl (Cbz), t-butoxycarbonyl (Boc) or sulfonamido groups (mesyl, Ms or tosyl, Ts).

SCHEME XI

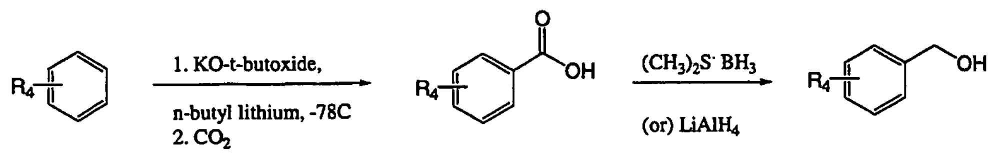


9 27 28

[0045] Synthetic Scheme XI illustrates a procedure used to prepare substituted 3-thiocoumaranones **28**. Thiophenols **9** are first treated with a base, such as NaOH, lithium diisopropyl amide (LDA) or sodium methoxide followed by condensation with ethyl bromoacetate in an appropriate solvent such as diethyl ether, ethanol, or tetrahydrofuran to provide the phenoxyacetate **27**. In step two, the ester group of **27** is hydrolyzed with aqueous sodium hydroxide and then treated with a mixture of

trifluoroacetic acid and trifluoroacetic anhydride to promote intramolecular Friedel-Crafts acylation affording 3-coumaranones derivatives **28**.

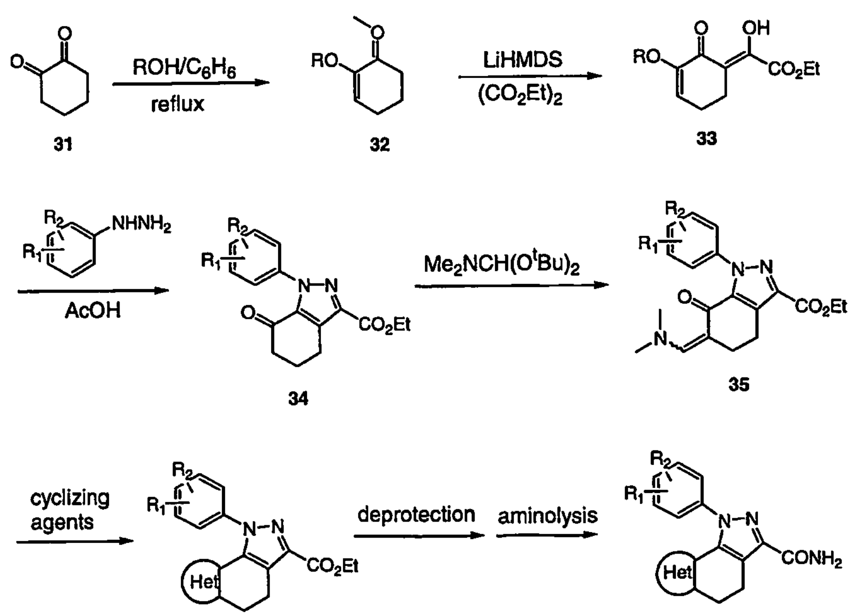
SCHEME XII



29 30 5

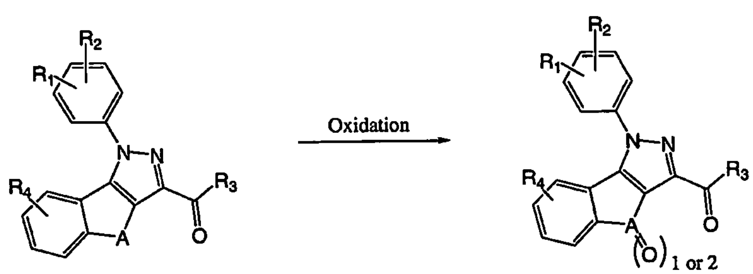
[0046] Synthetic Scheme XII illustrates a two step procedure used for the preparation of substituted benzyl alcohols **5**. In step one, a mixture of potassium tert-butoxide and anhydrous tetrahydrofuran, cooled to -78°C and treated with a 1.6 M solution of n-butyl lithium in hexanes, is added to an appropriate substituted benzene **29** the anion thereby generated is reacted with carbon dioxide to yield the benzoic acid **30**. In step two, the benzoic acid **30** is dissolved in a solvent, such as tetrahydrofuran, and treated with a reducing agent, such as borane dimethyl sulfide complex, to form the desired benzyl alcohol 5.

SCHEME XIII



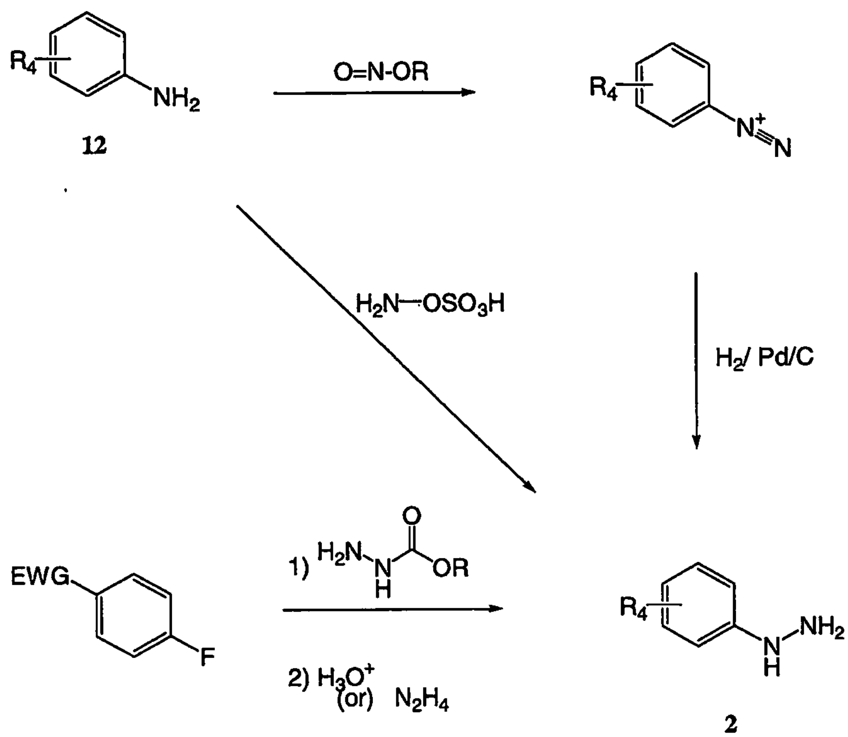
[0047] Scheme XIII describes the synthesis of the pyrazoles with fused heterocycles such as substituted pyrimdine and pyrazole. In step one, 1,2-cyclohexanedione (**31**) was refluxed with alcohols such as methanol or ethanol in benzene to provide the desired enone (**32**). In step two, enone **32** was treated with a base such as lithium bistrimethylsilylamide, followed by condensation with diethyl oxylate to afford 1,3-diketone (**33**). In step three, 1,3-diketone was allowed to react with a suitably substituted phenylhydrazine to form pyrazole **34**. Appropriate substituents could be; but are not limited to, methyl sulfone or sulfonamide, which may be protected. A suitable protecting group for the sulfonamide is 2,5-dimethylpyrrole. In step four, pyrazole was treated with dimethylformamide di-tert-butyl acetal to give enaminone **35**. In step five, enaminone was condensed with cyclizing agents such as hydrazine, guanidine, or thiourea to afford fused pyrazoles and pyrimidines **36**. In the final step, the ester was converted to amide **37** by treating with ammonium hydroxide in methanol. For compounds where the sulfonamide is protected with the 2,5-dimethylpyrrole, deprotection is achieved by treatment with refluxing trofluoroacetic acid and water.

SCHEME XIV



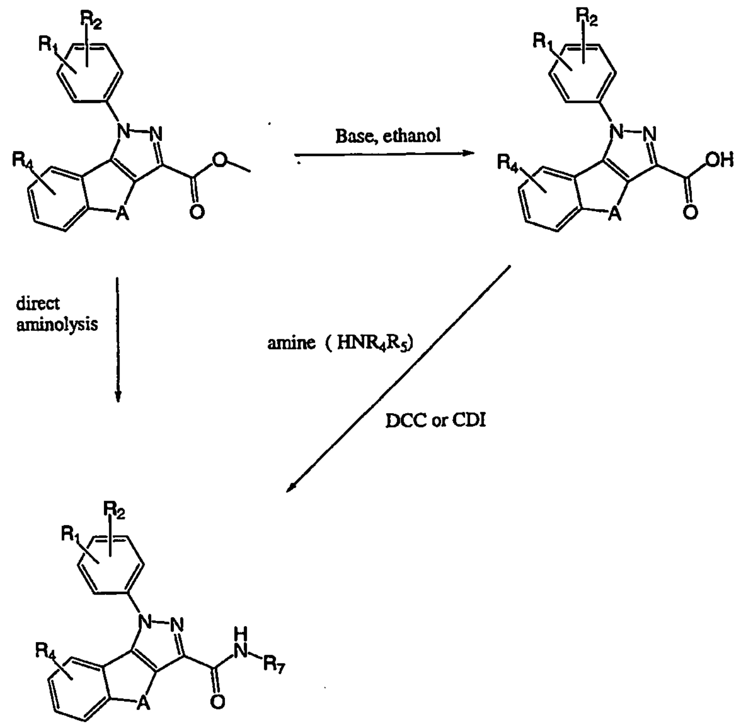
[0048] Synthetic Scheme XIV illustrates a procedure used for the preparation of the anti-inflammatory oxidized thio-containing fused tricyclic pyrazoles **3**. The appropriate pyrazole **3** from Scheme 1, where A is S or -$(CH_2)mS(CH_2)n$-, is treated with an oxidizing agent such as m-chloroperbenzoic acid (MCPBA), hydrogen peroxide, peracids, or potassium peroxymonosulfate. Compounds having differing amounts of oxidation (sulfinyls and sulfones) can be prepared by controlling the stoichiometry of oxidant to sulfide or separated by chromatography.

SCHEME XV



[0049] Scheme XV illustrates a method for the preparation of substituted arylhydrazines **2**. Anilines **12** can be treated with hydroxylamine-O-sulfonic acid to generate arylhydrazines **2** (JOC, *14*, 813, 1949). Anilines **12** can also be diazotized used sodium nitrite, or an alkyl nitrite, followed by catalytic reduction to generate arylhydrazines **2**. In selected cases, suitably activated aryl rings, such as; 4-fluoronitrobenzene or 4-fluorophenylmethylsulfone (EWG = electron withdrawing group; such as nitro or methylsulfone), can be converted to arylhydrazines via displacement of the fluorine with hydrazine or a carbazate, followed by hydrolysis of the protecting group.

SCHEME XVI



[0050] Synthetic Scheme XVI shows procedures for preparing anti-inflammatory agents **3** of Formula 1, wherein $R^3 = OCH_3$ is converted to OH or NHR^7. The esters **1** $R^3 = OCH_3$, which can be prepared as shown in Scheme I, is dissolved in aqueous methanol and a base such as 10% NaOH is added. The reaction is stirred at room temperature or heated to reflux to give the acids **3**, R^3 = OH. The acids **3**, R^3 = OH, can be converted to the appropriate amides **3**, $R^3 = NHR^7$, by dissolving in methanol and treating with an appropriate amine in the presence of a condensing agent such as dicyclohexylcarbodiimide (DCC) or carbonyl diimidazole (CDI). The amides **3**, $R^3 = NHR^7$ can also be prepared by direct aminolysis of **3**, $R^3 = OCH_3$.

[0051] The following examples contain detailed descriptions of the methods of preparation of compounds of Formula I. These detailed descriptions fall within the scope, and serve to exemplify, the above-described General Synthetic Procedures that form part of the invention. These detailed descriptions are presented for

illustrative purposes only and are not intended as a restriction on the scope of the invention. All parts are by weight and temperatures are in degrees centigrade unless otherwise indicated.

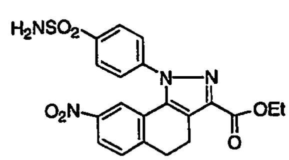
[0052] The compounds of the present invention may also be synthesized according to the methods of United States Patent 5,547,975.

[0053] The complete content of all publications, patents, and patent applications cited in this disclosure are herein incorporated by reference as if each individual publication, patent, or patent application were specifically and individually indicated to incorporated by reference. Although the foregoing invention has been described in some detail by way of illustration and example for the purposes of clarity of understanding, it will be readily apparent to one skilled in the art in light of the teachings of this invention that changes and modifications can be made without departing from the spirit and scope of the present invention. The following examples are provided for exemplification purposes only and are not intended to limit the scope of the invention, which has been described in broad terms above.

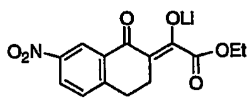
EXAMPLES

Example 1

Ethyl 1-{4-[(aminothio)peroxy]phenyl}-8-nitro-4,5-dihydro-1H-benzo[g]indazole-3-carboxylate



Step 1



[0054] To 7-nitro-1-tetralone (4.6 g, 0.024 mol) and ethyl oxalate (3.5 mL, 0.026 mol) in ether (100 mL) was added dropwise lithium bis(trimethylsilyl)amide (1M in THF, 26 mL). The slurry was stirred overnight and filtered to give the product as an olive green solid, 6.2 g (87% yield). ^{1}H NMR (DMSO-d_6/ 300 MHz) 8.45 (d, 1H); 8.05 (d of d, 1H); 7.42 (d, 1H); 4.08 (q, 2H); 2.82-2.72 (m, 2H); 2.51-2.43 (m, 2H); 1.21 (t, 3H).

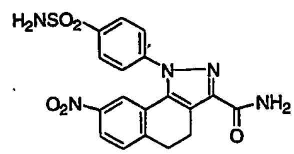
Step 2

[0055] The material of step 1 (6.2 g, 0.021 mol) and 4-sulfonamidophenylhydrazine hydrochloride (5.1 g, 0.023 mol) were stirred in methanol (100 mL) overnight. Conc HCl (2 mL) was added to the thick slurry and the contents were heated on a steam bath for 1 hour. Contents were allowed to cool and filtered to give an off-white solid, 6.9 g. NMR and LC/MS analysis show the solid to contain two components, the desired, and the hydrated pyrazole. TFA (60 mL) and TFAA (20 mL) were added to the solid and heated on a steam bath for 1 hour. Contents were concentrated *in vacuo* leaving the product as a solid, 6.4 g (69% yield). FABHRMS m/z 443.1020 (M+H, $C_{20}H_{19}N_4O_6S$ requires 443.1025). ^{1}H NMR (DMSO-d_6/ 300 MHz) 8.10 (d of d, 1H); 8.03 (d, 2H); 7.82 (d, 2H); 7.70 (d, 1H); 7.62 (s, 1H); 7.50 (d, 1H); 4.33 (q, 2H); 3.20-2.95 (m, 4H); 1.33 (t, 3H).

Anal. Calcd for $C_{20}H_{18}N_4O_6S$: C, 54.29; H, 4.10; N, 12.66. Found: C, 54.49; H, 4.00; N, 12.52.

Example 2

1-{4-[(aminothio)peroxy]phenyl}-8-nitro-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide

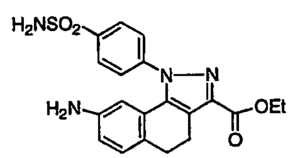


[0056] The final product of Example 1 (718 mg, 0.0016 mol), conc. ammonium hydroxide (30 mL), and methanol (15 mL) were stirred in a stoppered flask for 72 hours. Contents were filtered to give a light amber solid (606 mg). The solid was recrystallized from acetonitrile to give the product as a light amber solid , 450 mg (68% yield). FABHRMS m/z 414.0902 (M+H, $C_{18}H_{16}N_5O_5S$ requires 414.0872). ^{1}H NMR (DMSO-d_6/ 300 MHz) 8.15 - 7.95 (m, 3H); 7.83 (d, 2H); 7.80-7.40 (m, 6H); 3.20-2.95 (m, 4H).

Anal. Calcd for $C_{18}H_{15}N_5O_5S$: C, 52.30; H, 3.66; N, 16.94. Found: C, 52.04; H, 3.64; N, 16.61.

Example 3

ethyl 8-amino-1-[4-(aminosulfonyl)phenyl]-4,5-dihydro-1H-benzo[g]indazole-3-carboxylate

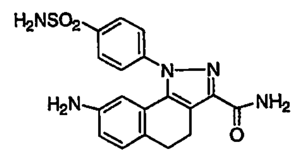


[0057] The final product of Example 1 (2.0 g) and 10% Pd/C (350 mg) in DMF (20 mL) were shaken at 55 PSI hydrogen for 3 hours. Contents were filtered and the filtrate was concentrated *in vacuo* leaving an amber wax. The wax was triturated with methanol and filtered to give the product as a light amber solid, 1.6 g (86% yield). FABHRMS m/z 413.1293 (M+H, $C_{20}H_{21}N_4O_4S$ requires 413.1284). ^{1}H NMR (DMSO-d_6/ 300 MHz) 8.00 (d, 2H); 7.73 (d, 2H); 7.50 (s, 2H); 7.01 (d, 1H); 6.43 (d of d, 1H); 6.00 (d, 1H); 4.83 (br s, 2H); 4.30 (q, 2H); 2.85-2.70 (m, 4H); 1.31 (t, 3H).

Anal. Calcd for $C_{20}H_{20}N_4O_4S$ (0.25 H_2O): C, 57.61; H, 4.96; N, 13.44. Found: C, 57.62; H, 5.11; N, 13.15.

Example 4

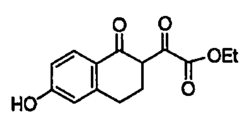
8-amino-1-{4-[(aminothio)peroxy]phenyl}-4,5-dihydro-1H-benzo[g]indazole-3-carboxamide



[0058] Example 4 was prepared similarly to Example 2 in 70 % yield. FABHRMS m/z 384.1136 (M+H, $C_{18}H_{18}N_5O_3S$ requires 384.1130). ^{1}H NMR (DMSO-d_6 / 300 MHz) 7.95 (d, 2H); 7.75 (d, 2H); 7.53 (br s, 1H); 7.43 (br s, 1H); 7.32 (br s, 1H); 7.01 (d, 1H); 6.44 (d of d, 1H); 6.03 (s, 1H); 4.81 (s, 2H); 2.93-2.65 (m, 4H).

[0059] Anal. Calcd for $C_{18}H_{17}N_5O_3S$: C, 56.38; H, 4.47; N, 18.27. Found: C, 56.31; H, 4.42; N, 18.31.

Example 5



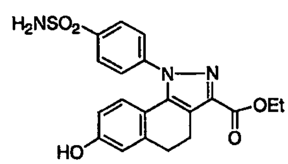
[0060] To 6-hydroxy-1-tetralone (10.4 g, 0.064 mol) and ethyl oxalate (17.4 mL, 0.128 mol) in THF (100 mL) was added dropwise lithium bis(trimethylsilyl)amide (1M in THF, 130 mL). The slurry was stirred overnight and a solid was filtered. The solid was dissolved in water and made acidic to pH 2.5 with 3 N HCl, precipitating a waxy solid. The waxy solid was extracted into EtOAc, dried ($MgSO_4$) and concentrated *in vacuo* leaving a dark solid (15.7 g). The

solid was purified by chromatography on silica gel, eluting with 15% EtOAc/hexanes to give a yellow solid (5.9 g). The solid was recrystallized from EtOAc/hexanes to give the product as a yellow solid, 3.7 g (22% yield). FABHRMS m/z 263.0925 (M+H, $C_{14}H_{15}O_5$ requires 263.0919). ^{1}H NMR ($CDCl_3$ / 300 MHz) 7.93 (d, 1H); 6.80 (d of d, 1H); 6.68 (s, 1H); 5.72 (s, 1H); 4.39 (q, 2H); 3.00-2.75 (m, 4H); 1.40 (t, 3H).

Anal. Calcd for $C_{14}H_{14}O_5$: C, 64.12; H, 5.38. Found: C, 63.79; H, 5.35.

Example 6

ethyl 1-[4-(aminosulfonyl)phenyl]-7-hydroxy-4,5-dihydro-1H-benzo[g]indazole-3-carboxylate

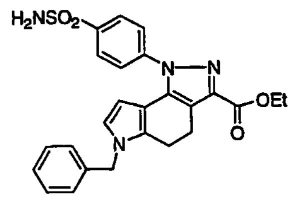


[0061] The material prepared in Example 5 (2.0 g, 0.0076 mol) and 4-sulfonamidophenylhydrazine hydrochloride (1.9 g, 0.0085) were stirred in glacial acetic acid (25 mL) for 96 hours. Contents were heated at 55°C for 5 hours, allowed to cool, diluted with water (75 mL), and filtered to give the product as a white solid, 3.1 g (90% yield). FABHRMS m/z 414.1146 (M+H, $C_{20}H_{20}N_3O_5S$ requires 414.1124). ^{1}H NMR (DMSO-d_6 / 300 MHz) 9.72 (s, 1H); 8.00 (d, 2H); 7.73 (d, 2H); 7.53 (s, 1H); 6.80 (s, 1H); 6.60-6.40 (m, 2H); 4.30 (q, 2H); 2.90 (s, 4H); 1.30 (t, 3H).

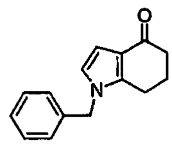
Anal. Calcd for $C_{20}H_{19}N_3O_5S$ (0.2 H_2O): C, 57.60; H, 4.69; N, 10.08. Found: C, 57.72; H, 4.91; N, 9.68.

Example 7

ethyl 1-[4-(aminosulfonyl)phenyl]-6-benzyl-1,4,5,6-tetrahydropyrrolo[2,3-g]indazole-3-carboxylate



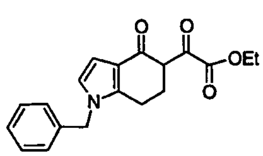
Step 1



[0062] To 1,5,6,7-tetrahydro-4H-indol-4-one (5.0 g, 0.037 mol) in DMF (20 mL) was added benzyl chloride (4.4 mL, 0.038 mol) and potassium carbonate (5.3 g, 0.038 mol). Contents were heated at 70°C overnight. Contents were allowed to cool and partitioned between EtOAc and water. The EtOAc layer was dried ($MgSO_4$) and concentrated *in vacuo* leaving an amber oil, 7.9g. The oil was purified by chromatography on silica gel eluting with 25% EtOAc/hexanes to give the desired as a white solid, 7.1 g (85% yield). FABHRMS m/z 226.1213 (M+H, $C_{15}H_{16}NO$ requires 226.1232). ^1H NMR ($CDCl_3$ / 300 MHz) 7.40-7.28 (m, 3H); 7.10-7.00 (m, 2H); 6.63-6.53 (m, 2H); 5.02 (s, 2H); 2.70-2.60 (m, 2H); 2.50-2.40 (m, 2H); 2.10-2.06 (m, 2H).

Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.90; H, 6.65; N, 6.09.

Step 2



[0063] The product of step 2 was prepared similarly to Example 5 starting with the material of step 1 in 67% yield. FABHRMS m/z 326.1393 (M+H, $C_{19}H_{20}NO_4$

requires 326.1392). ^{1}H NMR ($CDCl_3$ / 300 MHz) 7.40-7.26 (m, 3H); 7.10-7.00 (m, 2H); 6.70-6.60 (m, 2H); 5.06 (s, 2H); 4.33 (q, 2H); 3.20-3.08 (m, 2H); 2.75-2.60 (m, 2H); 1.40 (t, 3H).

Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.09; H, 5.75; N, 4.08.

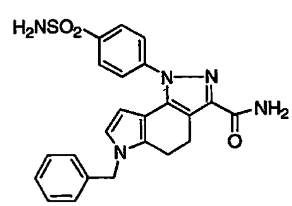
Step 3

[0064] The final product of Example 7 was prepared similarly to Example 6 starting with the product of step 2 in 37% yield. FABHRMS m/z 477.1609 (M+H, $C_{25}H_{25}N_4O_4S$ requires 477.1596). ^{1}H NMR (DMSO-d_6 / 300 MHz) 8.00 (d, 2H); 7.80 (d, 2H); 7.50 (s, 1H); 7.40-7.20 (m, 3H); 7.20-7.05 (m, 2H); 6.80 (s, 1H); 5.62 (s, 1H); 5.13 (s, 2H); 4.25 (q, 2H); 3.10-2.92 (m, 2H); 2.89-2.70 (m, 2H); 1.30 (t, 3H).

Anal. Calcd for $C_{25}H_{24}N_4O_4S$: C, 63.01; H, 5.08; N, 11.76. Found: C, 62.95; H, 5.02; N, 11.76.

Example 8

1-[4-(aminosulfonyl)phenyl]-6-benzyl-1,4,5,6-tetrahydropyrrolo[2,3-g]indazole-3-carboxamide



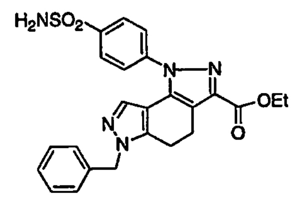
[0065] Example 8 was prepared similarly to Example 2 starting with the compound of Example 7 in 75% yield. FABHRMS m/z 448.1477 (M+H, $C_{23}H_{22}N_5O_3S$ requires 448.1443). ^{1}H NMR (DMSO-d_6 / 300 MHz) 8.00 (d, 2H);

7.80 (d, 2H); 7.60-7.15 (m, 3H); 7.10 (d, 2H); 6.79 (d, 1H); 5.65 (d, 1H); 5.12 (s, 2H); 3.10-2.93 (m, 2H); 2.82-2.68 (m, 2H).

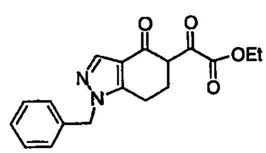
Anal. Calcd for $C_{23}H_{21}N_5O_3S$: C, 61.73; H, 4.73; N, 15.65. Found: C, 61.33; H, 4.52; N, 15.43.

Example 9

ethyl 1-[4-(aminosulfonyl)phenyl]-6-benzyl-1,4,5,6-tetrahydropyrazolo[3,4-e]indazole-3-carboxylate



Step 1



[0066] The product of step 1 was prepared similarly to Example 5 starting with 1,5,6,7-tetrahydro-1-(phenylmethyl)indazol-4-one [*Heterocycles*, 32 (1) 41-72 (1991)] in 89% yield. FABHRMS m/z 327.1347 (M+H, $C_{18}H_{19}N_2O_4$ requires 327.1345). ^{1}H NMR ($CDCl_3$ / 300 MHz) 8.00 (s, 1H); 7.40-7.30 (m, 3H); 7.13 (d, 2H); 5.30 (s, 2H); 4.31 (q, 2H); 3.19-3.03 (m, 2H); 2.80-2.68 (m, 2H); 1.38 (t, 3H).

Anal. Calcd for $C_{18}H_{18}N_2O_4$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.35; H, 5.47; N, 8.78.

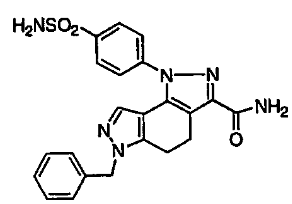
Step 2

[0067] The final product of Example 9 was prepared similarly to Example 6 starting with the compound of step 1 in 64% yield. FABHRMS m/z 478.1549 (M+H, $C_{24}H_{24}N_5O_4S$ requires 478.1551). ^{1}H NMR (DMSO-d_6 / 300 MHz) 8.02 (d, 2H); 7.82 (d, 2H); 7.51 (s, 1H); 7.40-7.22 (m, 3H); 7.21-7.13 (m, 2H); 7.10 (s, 1H); 5.40 (s, 2H); 4.30 (q, 2H); 3.20-2.90 (m, 4H); 1.30 (t, 3H).

Anal. Calcd for $C_{24}H_{23}N_5O_4S$: C, 60.36; H, 4.85; N, 14.67. Found: C, 60.60; H, 4.86; N, 14.71.

Example 10

1-[4-(aminosulfonyl)phenyl]-6-benzyl-1,4,5,6-tetrahydropyrazolo[3,4-e]indazole-3-carboxamide

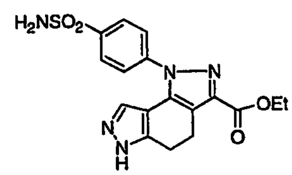


[0068] Example 10 was prepared similarly to Example 2 starting with the product of Example 9 in 79% yield. FABHRMS m/z 449.1399 (M+H, $C_{22}H_{21}N_6O_3S$ requires 449.1396). ^{1}H NMR (DMSO-d_6 / 300 MHz) 8.00 (d, 2H); 7.84 (d, 2H); 7.60-7.40 (m, 2H); 7.40-7.22 (m, 3H); 7.25-7.10 (m, 2H); 5.37 (s, 2H); 3.20-2.90 (m, 4H).

Anal. Calcd for $C_{22}H_{20}N_6O_3S$ (0.8 H_2O): C, 57.08; H, 4.70; N, 18.15. Found: C, 57.54; H, 4.56; N, 17.77.

Example 11

ethyl 1-[4-(aminosulfonyl)phenyl]-1,4,5,6-tetrahydropyrazolo[3,4-e]indazole-3-carboxylate

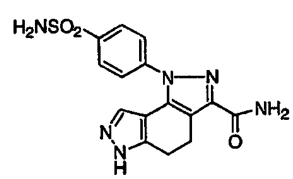


[0069] The material of Example 9 (4.2 g, 0.009 mol), DMF (40 mL), glacial acetic acid (20 mL), and Pearlman's catalyst (1.5 g) were shaken at 55 psi hydrogen for 96 hours. Contents were filtered through celite and the filtrate was concentrated *in vacuo* leaving the product as a gray solid, 2.4 g (70% yield). FABHRMS m/z 388.1124 (M+H, $C_{17}H_{18}N_5O_4S$ requires 388.1080). ^{1}H NMR (DMSO-d_6/ 300 MHz) 8.02 (d, 2H); 7.80 (d, 2H); 7.60 (br s, 1H); 7.30 (s, 1H); 4.35 (q, 2H); 3.15-3.00 (m, 2H); 3.00-2.80 (m, 2H); 1.32 (t, 3H).

Anal. Calcd for $C_{17}H_{17}N_5O_4S$: C, 52.70; H, 4.42; N, 18.08. Found: C, 52.47; H, 4.18; N, 17.89.

Example 12

1-[4-(aminosulfonyl)phenyl]-1,4,5,6-tetrahydropyrazolo[3,4-e]indazole-3-carboxamide

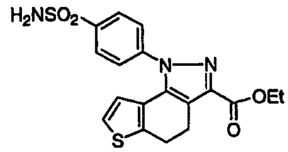


[0070] Example 12 was prepared similarly to Example 2 starting with the material of 11in 86% yield. FABHRMS m/z 359.0939 (M+H, $C_{15}H_{15}N_6O_3S$ requires 359.0926). ^{1}H NMR (DMSO-d_6/ 300 MHz) 8.02 (d, 2H); 7.87 (d, 2H); 7.56 9s, 1H); 7.50 (br s, 2H); 7.35 (s, 2H); 3.20-3.00 (m, 2H); 2.95-2.80 (m, 2H).

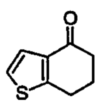
[0071] Anal. Calcd for $C_{15}H_{14}N_6O_3S$: C, 50.27; H, 3.94; N, 23.45. Found: C, 50.07; H, 3.73; N, 23.08.

Example 13

ethyl 1-[4-(aminosulfonyl)phenyl]-4,5-dihydro-1H-thieno[2,3-g]indazole-3-carboxylate

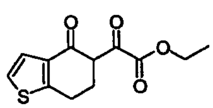


Step 1



[0072] 4-(2-Thienyl)butyric acid (9.7 g, 0.057 mol), acetic anhydride (12 mL), and phosphoric acid (85%, 0.25 mL) were refluxed for 3 hours. Contents were allowed to cool and partitioned between EtOAc and water. The EtOAc layer was dried ($MgSO_4$) and concentrated *in vacuo* leaving a dark oil, 9.0 g. The oil was distilled on a kugelrohr apparatus at 50°C (0.1 mm) to give a white solid, 5.0 g (58% yield). ^{1}H NMR ($CDCl_3$/ 300 MHz) 7.37 (d, 1H); 7.02 (d, 1H); 3.08-2.95 (m, 2H); 2.60-2.50 (m, 2H); 2.30-2.10 (m, 2H).

Step 2



[0073] The product of step 2 was prepared similarly to step 1 of Example 1 using the material of step 1 in 77% yield. ^{1}H NMR (DMSO-d_6 / 300 MHz) 7.32-7.05 (m, 2H); 4.05 (q, 2H); 2.85-2.50 (m, 4H); 1.20 (t, 3H).

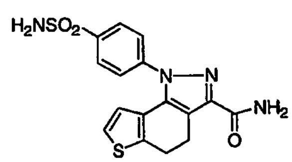
Step 3

[0074] The final product of Example 13 was prepared similarly to Example 6 starting with the material of step 2 in 86% yield. FABHRMS m/z 404.0702 (M+H, $C_{18}H_{18}N_3O_4S_2$ requires 404.0739). ^{1}H NMR (DMSO-d_6 / 300 MHz) 8.05 (d, 2H); 7.70 (d, 2H); 7.59 (s, 1H); 7.39 (d, 1H); 6.40 (d, 1H); 4.35 (q, 2H); 3.10 (s, 4H); 1.35 (t, 3H).

Anal. Calcd for $C_{18}H_{17}N_3O_4S_2$: C, 53.58; H, 4.25; N, 10.41. Found: C, 53.51; H, 4.02; N, 10.45.

Example 14

1-[4-(aminosulfonyl)phenyl]-4,5-dihydro-1H-thieno[2,3-g]indazole-3-carboxamide

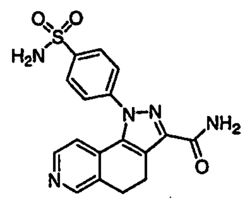


[0075] Example 14 was prepared similarly to Example 2 staring with the compound of Example 13 in 85% yield. FABHRMS m/z 375.0601 (M+H, $C_{16}H_{15}N_4O_3S_2$ requires 375.0586). ^{1}H NMR (DMSO-d_6 / 300 MHz) 8.05 (d, 2H); 7.70 (d, 2H); 7.59 (s, 1H); 7.55 (s, 2H); 6.47 (d, 1H); 3.10 (s, 4H).

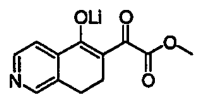
Anal. Calcd for $C_{16}H_{14}N_4O_3S_2$: C, 56.06; H, 4.70; N, 13.08. Found: C, 56.49; H, 4.74; N, 13.21.

Example 15

1-[4-(aminosulfonyl)phenyl]-4,5-dihydro-1H-pyrazolo[3,4-f]isoquinoline-3-carboxamide

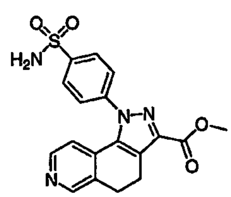


Step 1



[0076] To 7,8-Dihydroisoquinolin-5(6H)-one (1.17 gm, 8 mmol) in diethyl ether (50 mL) was added 1M LHMDS (8 mL, 8 mmol) dropwise over several minutes (cf. Lardenois, P.; et al. Synthetic Communications **26(12)**, 2305-8, 1996). A precipitate slowly formed and the reaction became light yellow. After about 15 minutes, dimethyl oxalate (944 mg, 8 mmol) was added as a solid and the reaction stirred at room temperature for 72 hours. The resulting precipitate was collected by suction filtration and washed extensively with diethyl ether. A bright yellow solid was obtained. Yield; 1.7 gm (89%). ^{1}H-NMR (d_6-DMSO) 2.41 (t, 2H); 2.63 (t, 2H); 3.56 (s, 3H); 7.51 (d, 1H); 8.37 (s, 1H); 8.40 (d, 1H).

[0077] Step 2



[0078] The enolate from step 1 (717 mg, 3 mmol) was combined with 4-sulfonamidophenyl-hydrazine hydrochloride (669 mg, 2 mmol) in methanol (10 mL) and stirred at ambient temperature for 72 hours, then the resulting precipitate was collected by suction filtration and washed with methanol. The resulting hydrated pyrazole (502 mg) was re-suspended in methanol and concentrated HCl

(0.5 mL) was added. The reaction was stirred at ambient temperature for two hours, then concentrated to a yellow solid in-vacuo. The solid was triturated with methanol and collected by suction filtration. Yield 250 mg (22 %). ^{1}H-NMR (d_6-DMSO) 3.09 (s, 4H); 3.87 (s, 3H); 6.91 (d, 1H); 7.60 (s, 2H); 7.84 (d, 2H); 8.03 (d, 2H); 8.50 (d, 1H); 8.80 (s, 1H). FABHRMS m/z 385.0987 (M+H, $C_{18}H_{17}N_4O_4S$ requires 385.0971).

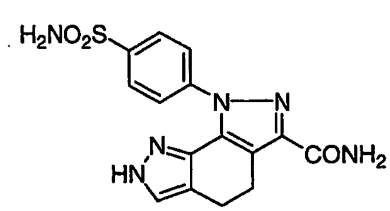
[0079] Step 3

The methyl ester from step 2 (240 mg, 0.625 mmol) was suspended in methanol (10 mL) and concentrated ammonium hydroxide (2 mL) was added. The reaction was heated to 95 C in a sealed tube for 16 hours. The reaction was cooled and concentrated to a reddish solid, which was triturated with methanol. ^{1}H-NMR suggested some carboxylic acid may be present, so the solid was dissolved in methanol (15mL) and 1 N HCl (3 mL). The homogeneous solution was then made basic with saturated $NaHCO_3$ solution to pH = 8. After concentrating the solution under a stream of nitrogen, a brown solid was collected (100 mg). This solid was filtered through a plug of silica gel (10 gm) using 10% methanol/dichloromethane to obtain an off white solid. Yield: 90 mg (39 %). FABHRMS m/z 370.0966 (M+H, $C_{17}H_{16}N_5O_3S$ requires 370.0974).

^{1}H-NMR (d_4-MeOH + TFA) 3.25 (s, 4H); 7.25 (d, 1H); 7.83 (d, 2H); 8.14 (d, 2H); 8.49 (d, 1H); 8.79 (s, 1H).

Example 16

1-[4-(aminosulfonyl)phenyl]-1,4,5,8-tetrahydropyrazolo[4,3-g]indazole-3-carboxamide



Step 1

[0080] A mixture of 1,2-cyclohexanedione (26.0 g) and ethanol (100 mL) in 500 mL of benzene was heated at reflux with a Dean-Stark trap overnight. After the removal of solvent, the residue was purified by chromatography on silica gel (ethyl acetate/hexane, 2:8) to give 15.3 g of the desired 2-ethoxy-2-cyclohexen-1-one as a light yellow oil (47% yield). To 120 mL 1.0 M solution of LiHMDS in THF was added a solution of the above compound (15.3 g, 0.11 mol) in 100 mL of ether at –78°C. After the addition, the dark brown mixture was stirred at this temperature for ½ h, a solution of diethyl oxylate (17.5 g, 0.12 mol) in 30 mL of ether was added in one portion. The reaction was allowed to warm up to room temperature over 18 h. Water was added and acidified to pH = 4 with 1 N HCl. The aqueous phase was extracted with ethyl acetate and the organic layer was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated to afford 21.5 g of product as a dark brown liquid that was used without further purification.

Step 2

[0081] A mixture of the crude from step 1 (20.0 g, 0.083 mol) and 1-(4-hydrazinophenylsulfonyl)-2,5-dimethylpyrrole (22.0 g, 0.083 mol) in 400 mL of acetic acid was stirred at room temperature overnight. The solvent was removed and the residue was partitioned between ethyl acetate and conc. ammonium hydroxide. The organic layer was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated and the residue was purified by chromatography on silica gel (ethyl acetate/ hexane, 3:7) to give 16.2 g of pure product as a yellow solid,

Step 3

[0082] A mixture of the product from step 2 (3.1 g, 0.0062 mol) and N, N-dimethylformamide di-tert-butyl acetal (10.2 g, 0.062 mol) was heated at reflux overnight. After cooling, excess reagent was removed under vacuum and the

residue was triturated with cold ethanol to give 2.3 g of pure product as a yellow solid (77% yield); mp: 230-231°C; Anal. Calcd. for $C_{25}H_{28}N_4O_5S$: C, 60.47; H, 5.68; N, 11.28; S, 6.46. Found: C, 59.98; H, 5.42; N, 10.93; S, 6.11.

Step 4

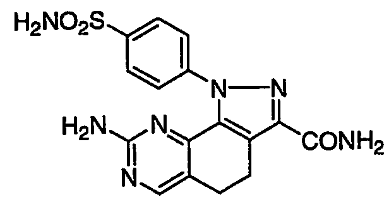
[0083] To a suspension of the product from step 3 (0.45 g, 0.0009 mol) in 10 mL of ethanol was added hydrazine (0.03 mL, 0.0009 mol) and the mixture was stirred at reflux overnight. Solvent was removed and the residue was purified by chromatography on silica gel (ethyl acetate/hexane, 2:8) to give 0.38 g of product as a yellow solid (93% yield); mp: 134-136°C; Anal. Calcd. for $C_{23}H_{23}N_5O_4S$: C, 59.34; H, 4.98; N, 15.04; S, 6.89. Found: C, 59.28; H, 4.95; N, 14.76; S, 6.93.

Step 5

[0084] The product from step 4 (0.35 g, 0.00075 mol) was treated with a mixture of TFA (15 mL) and water (5 mL) and the dark brown solution was refluxed under nitrogen for 2 h. Cooled and basified with conc. ammonium hydroxide to precipitate out 0.18 g of crude product as a pale yellow solid. A suspension of this solid in a mixture of conc. ammonium hydroxide (15 mL) and methanol (5 mL) was stirred at RT for 3 days. Solvent was removed to half volume and the solid was filtered to afford 0.1 g of product was white powder (50% yield for two steps); mp: 347°C (decomp); Anal. Calcd. for $C_{15}H_{14}N_6O_3S$: C, 50.27; H, 3.94; N, 23.45; S, 8.95. Found: C, 49.65; H, 3.81; N, 22.78; S, 8.77.

Example 17

8-amino-1-[4-(aminosulfonyl)phenyl]-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide



Step 1

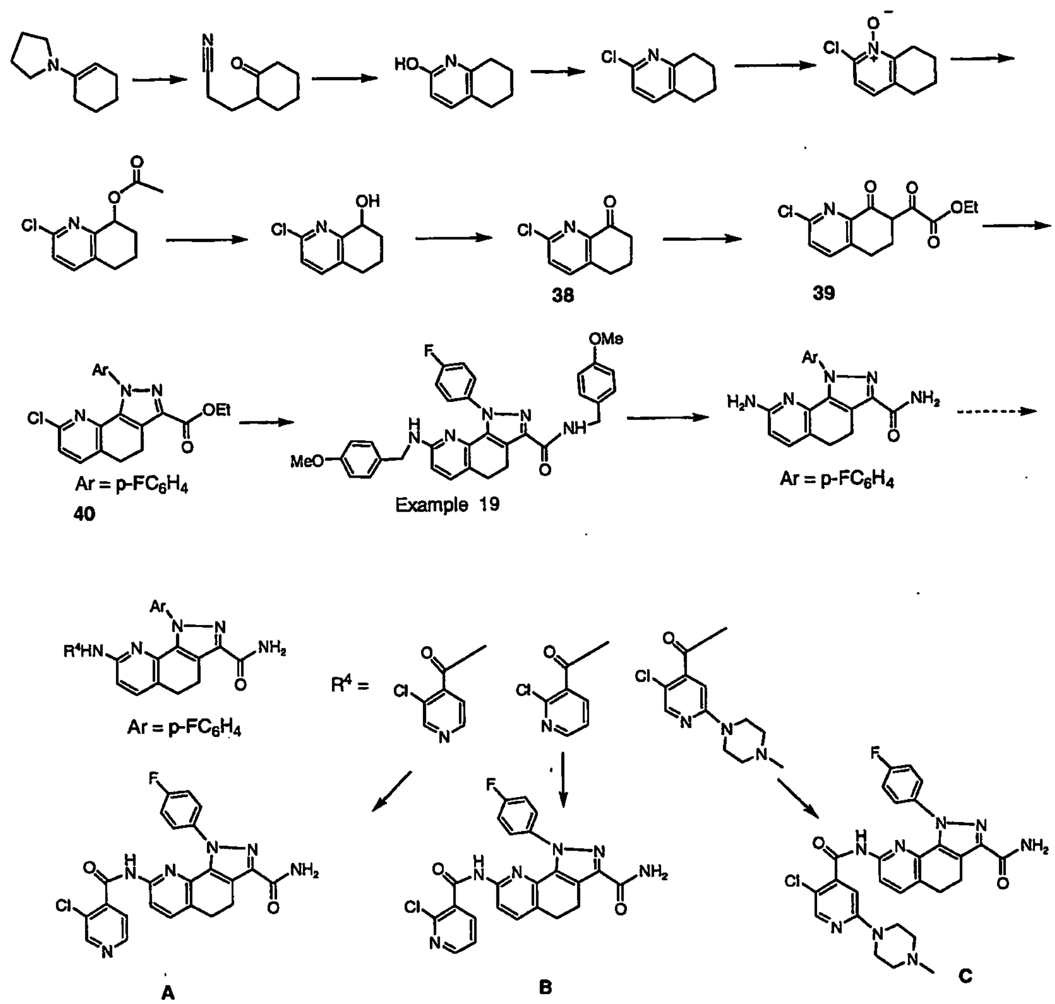
[0085] To a suspension of the product from step 3 of Example 16 (8.7 g, 0.018 mol) and guanidine hydrochloride (1.7 g, 0.018 mol) in 250 mL of ethanol, was added sodium ethoxide (1.22 g, 0.018 mol) and the mixture was refluxed under nitrogen overnight. After the removal of solvent, the residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated and the crude was purified by chromatography on silica gel (ethyl acetate/hexane, 3:7) to give 5,2 g of product as brown solid (60% yield); mp: 111-112°C; Anal. Calcd. for $C_{24}H_{24}N_6O_4S$: C, 58.52; H, 4.91; N, 17.06; S, 6.51. Found: C, 58.24; H, 4.84; N, 16.80; S, 6.68.

Step 2

[0086] This compound was synthesized by following the same procedure as step 5 in Example 1 in 52% yield; mp: 332°C (decomp); Anal. Calcd. for $C_{16}H_{15}N_7O_3S$: C, 49.86; H, 3.92; N, 25.44; S, 8.32. Found: C, 49.49; H, 3.86; N, 25.52; S, 7.93.

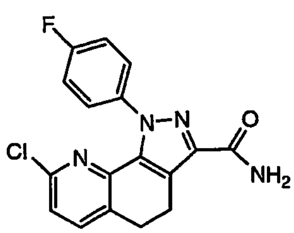
[0087] Examples 18, and 19 were prepared according to Scheme XVIII. Related compounds such as A, B and C shown in Scheme XVIII can be prepared in a similar manner using the appropriate R^4 group.

SCHEME XVIII



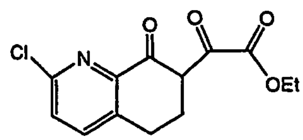
Example 18

8-Chloro-1-(4-fluorophenyl)-4,5-dihydro-1H-pyrazolo[4,3-h]quinoline-3-carboxamide



Step 1

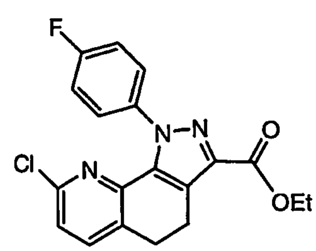
Ethyl (2-chloro-8-oxo-5,6,7,8-tetrahydroquinolin-7-yl)(oxo)acetate



[0088] To a suspension of 10.8 g of 2-chloro-6,7-dihydroquinolin-8(5H)-one **38** in 30 ml of anhydrous ethanol, cooled to about 10^0 C, 24.4 ml of a 21 wt% solution of sodium ethoxide (65.46 mmol) in anhydrous ethanol (24.4 ml) was added dropwise with stirring under nitrogen atmosphere for 10 minutes. After 5 minutes 8.82 g of diethyl oxalate (59.54 mmol) was added over 2 minutes. The reaction mixture was stirred at 10^0 C for 30 minutes, then 1 hour at room temperature. To the reaction mixture, cooled to about 0^0 C, 66 ml of a 1M solution of HCl in ethanol was added dropwise for 10 minutes. A white precipitate was separated by filtration and washed with 30 ml of chloroform. The organic portions were combined and solvents were removed to give 16.5 g (99% yield) of the crude desired product **39**, which was used in following synthesis without additional purification. ^{1}H NMR (300 MHz, δ, $DCCl_3$): 1.45 (t, 3H, J = 7.15 Hz), 2.88-3.02 (m, 4H), 4.44 (q, 2H, J = 7.15 Hz), 7.43 (d, 1H, J = 8.05 Hz), 7.62 (d, 1H, J = 8.05 Hz), 13.6-14.2 (1H, broad). ESI mass spectrum for $(C_{13}H_{12}ClNO_4 + 1)^+$: 282.1

Step 2

Ethyl 8-chloro-1-(4-fluorophenyl)-4,5-dihydro-1H-pyrazolo[4,3-h]quinoline-3-carboxylate

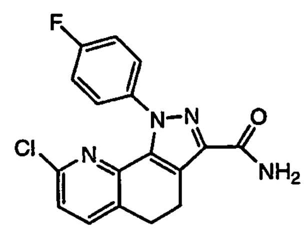


[0089] The mixture of ethyl (2-chloro-8-oxo-5,6,7,8-tetrahydroquinolin-7-

yl)(oxo)acetate **39** from step 1 (13 g, 46.15 mmol) and 4-fluorophenylhydrazine hydrochloride (7.51 g, 46.15 mmol) in 500 ml of 1M solution of HCl in ethanol was placed in 1 L flask with a condenser under nitrogen atmosphere and heated at reflux for 1 hour. Then, it was cooled to room temperature and placed in refrigerator overnight at -5^0 C. The white crystalline precipitate was filtered and washed with ether to give 12.3 g of ethyl 8-chloro-1-(4-fluorophenyl)-4,5-dihydro-1H-pyrazolo[4,3-h]quinoline-3-carboxylate **40** (71% yield). It was used in following synthesis without additional purification. ^{1}H NMR (300 MHz, δ, $DCCl_3$): 1.48 (t, 3H, J = 7.15 Hz), 3.01-3.25 (m, 4H), 4.49 (q, 2H, J = 7.15 Hz), 7.10-7.24 (m, 3H), 7.50-7.62 (m, 3H). ESI mass spectrum for $(C_{19}H_{15}ClFN_3O_2 + 1)^+$: 372.1

Step 3

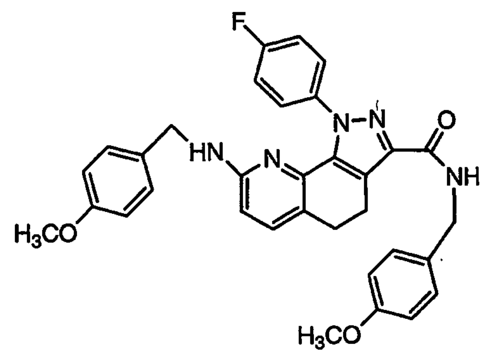
8-Chloro-1-(4-fluorophenyl)-4,5-dihydro-1H-pyrazolo[4,3-h]quinoline-3-carboxamide



[0090] A mixture of 1 g of ethyl 8-chloro-1-(4-fluorophenyl)-4,5-dihydro-1H-pyrazolo[4,3-h]quinoline-3-carboxylate **40** from step 2, 25 ml of methanol, and 25 ml of liquid ammonia were placed in an autoclave and stirred overnight at 130^0 C. After cooling to room temperature and removing ammonia, a suspension of gray crystalline precipitate in methanol was obtained. The solid was isolated by filtration to give 0.8 g (87% yield) of 8-chloro-1-(4-fluorophenyl)-4,5-dihydro-1H-pyrazolo[4,3-h]quinoline-3-carboxamide. ^{1}H NMR (400 MHz, δ, $DCCl_3$): 3.01-3.25 (m, 4H), 5.38 (s, 1H), 6.81 (s, 1H), 7.09 (d, 1H, J = 7.9 Hz) 7.11-7.19 (m, 2H), 7.45-7.56 (m, 3H). ESI mass spectrum for $(C_{17}H_{12}ClFN_4O + 1)^+$: 343.1

Example 19

1-(4-Fluorophenyl)-N-(4-methoxybenzyl)-8-[(4-methoxybenzyl)amino]-4,5-dihydro-1H-pyrazolo[4,3-h]quinoline-3-carboxamide



[0091] Ethyl 8-chloro-1-(4-fluorophenyl)-4,5-dihydro-1H-pyrazolo[4,3-h]quinoline-3-carboxylate **40** (3.8 g, 10.22 mmol) in 35 ml of 4-methoxybenzylamine was heated at 185^0 C for 26 hours. The reaction mixture contained the title compound as a major product. It was isolated by thin layer silica chromatography (ethyl acetate-hexane 60:40). ^{1}H NMR (400 MHz, δ, $DCCl_3$): 2.86-292 (m, 2H), 3.14-3.21 (m, 2H), 3.76-3.78 (m, 6H), (3.95 (d, 2H, J = 5.9 Hz), 4.28 (t, 1H, J = 5.8 Hz), 4.54 (d, 2H, J = 5.9 Hz), 6.20 (d, 1H, J = 8.2 Hz), 6.78-6.86 (m, 4H), 6.93-7.02 (m, 2H), 7.01-7.06 (m, 2H), 7.20 (t, 1H, J = 5.64), 7.26-7.30 (m, 3H), 7.42-7.48 (m, 2H). ESI mass spectrum for $(C_{33}H_{30}FN_5O_3 + 1)^+$: 564.2

[0092] Table 1 shows the bioactivity for the exemplified compounds as measured in the IKK heterodimer Resin Enzyme Assay expressed as LC50.

TABLE 1

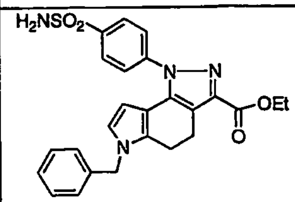
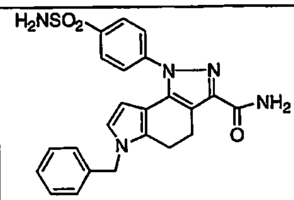
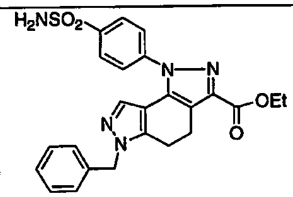
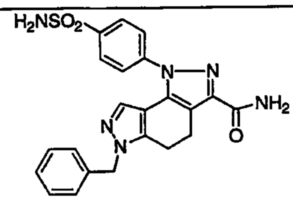
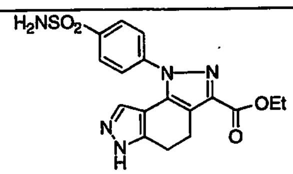
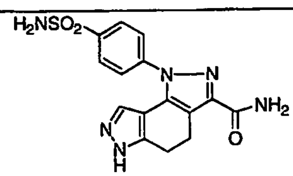
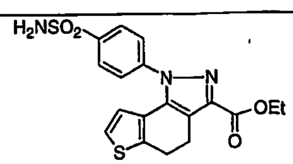
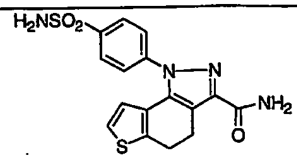
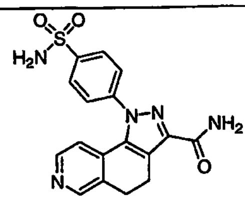
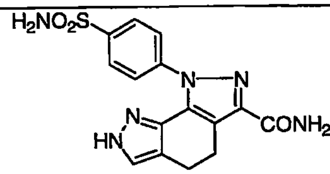
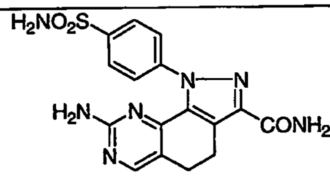
COMPOUND	STRUCTURE	EXAMPLE	HetD
ethyl 1-[4-(aminosulfonyl)phenyl]-6-benzyl-1,4,5,6-tetrahydropyrrolo[2,3-g]indazole-3-carboxylate		Example 7	>200 µM
1-[4-(aminosulfonyl)phenyl]-6-benzyl-1,4,5,6-tetrahydropyrrolo[2,3-g]indazole-3-carboxamide		Example 8	>200 µM
ethyl 1-[4-(aminosulfonyl)phenyl]-6-benzyl-1,4,5,6-tetrahydropyrazolo[3,4-e]indazole-3-carboxylate		Example 9	>200 µM
1-[4-(aminosulfonyl)phenyl]-6-benzyl-1,4,5,6-tetrahydropyrazolo[3,4-e]indazole-3-carboxamide		Example 10	>200 µM
ethyl 1-[4-(aminosulfonyl)phenyl]-1,4,5,6-tetrahydropyrazolo[3,4-e]indazole-3-carboxylate		Example 11	>200 µM
1-[4-(aminosulfonyl)phenyl]-1,4,5,6-tetrahydropyrazolo[3,4-e]indazole-3-carboxamide		Example 12	0.67 µM
ethyl 1-[4-(aminosulfonyl)phenyl]-4,5-dihydro-1H-thieno[2,3-g]indazole-3-carboxylate		Example 13	>200 µM

TABLE 1 cont

COMPOUND	STRUCTURE	EXAMPLE	HetD
1-[4-(aminosulfonyl)phenyl]-4,5-dihydro-1H-thieno[2,3-g]indazole-3-carboxamide		Example 14	3.2 µM
1-[4-(aminosulfonyl)phenyl]-4,5-dihydro-1H-pyrazolo[3,4-f]isoquinoline-3-carboxamide		Example 15	8.21 µM
1-[4-(aminosulfonyl)phenyl]-1,4,5,8-tetrahydropyrazolo[4,3-g]indazole-3-carboxamide		Example 16	0.96 µM
8-amino-1-[4-(aminosulfonyl)phenyl]-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide		Example 17	2.3 µM

[0093] In a likewise manner the following compounds of Table 2 could also be prepared.

TABLE 2

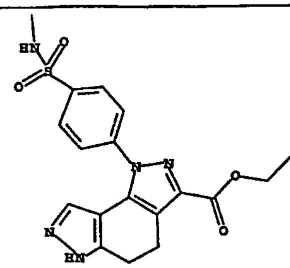
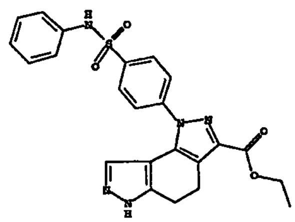
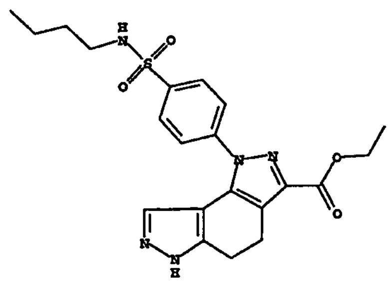
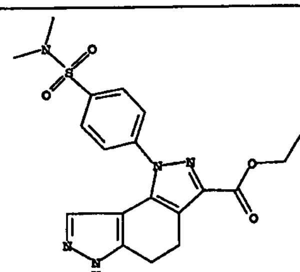
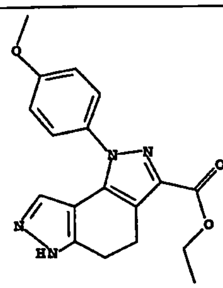
Ethyl 1-{4-[(methylamino)sulfonyl]phenyl}-1,4,5,6-tetrahydropyrazolo[3,4-e]indazole-3-carboxylate	
Ethyl 1-[4-(anilinosulfonyl)phenyl]-1,4,5,6-tetrahydropyrazolo[3,4-e]indazole-3-carboxylate	
Ethyl 1-{4-[(butylamino)sulfonyl]phenyl}-1,4,5,6-tetrahydropyrazolo[3,4-e]indazole-3-carboxylate	
ethyl 1-{4-[(dimethylamino)sulfonyl]phenyl}-1,4,5,6-tetrahydropyrazolo[3,4-e]indazole-3-carboxylate	
ethyl 1-(4-methoxyphenyl)-1,4,5,6-tetrahydropyrazolo[3,4-e]indazole-3-carboxylate	

TABLE 2 cont

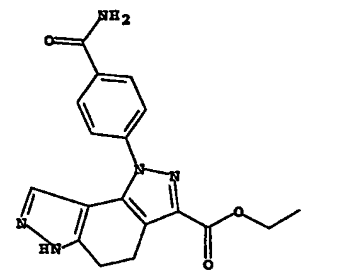
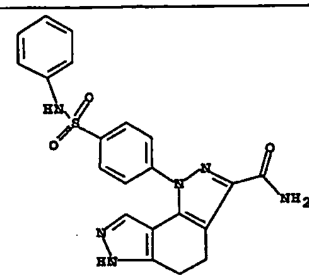
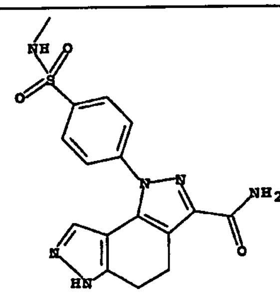
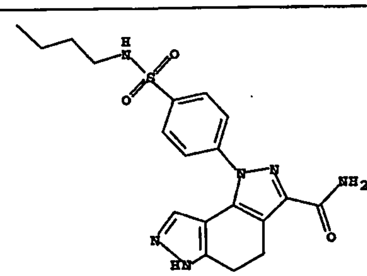
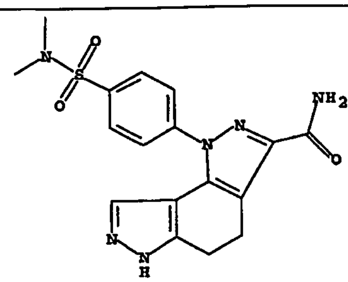
Ethyl 1-[4-(aminocarbonyl)phenyl]-1,4,5,6-tetrahydropyrazolo[3,4-e]indazole-3-carboxylate	
1-[4-(anilinosulfonyl)phenyl]-1,4,5,6-tetrahydropyrazolo[3,4-e]indazole-3-carboxamide	
1-{4-[(methylamino)sulfonyl]phenyl}-1,4,5,6-tetrahydropyrazolo[3,4-e]indazole-3-carboxamide	
1-{4-[(butylamino)sulfonyl]phenyl}-1,4,5,6-tetrahydropyrazolo[3,4-e]indazole-3-carboxamide	
1-{4-[(dimethylamino)sulfonyl]phenyl}-1,4,5,6-tetrahydropyrazolo[3,4-e]indazole-3-carboxamide	

TABLE 2 cont

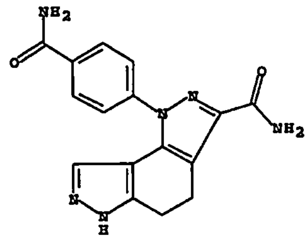
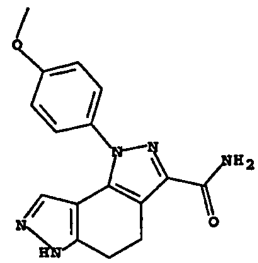
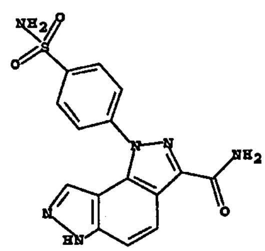
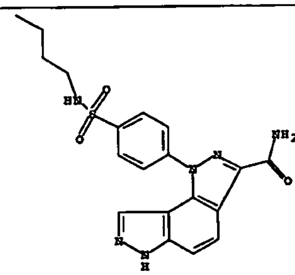
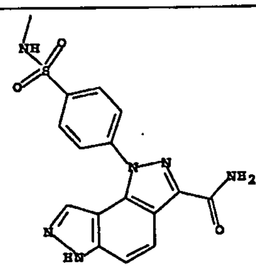
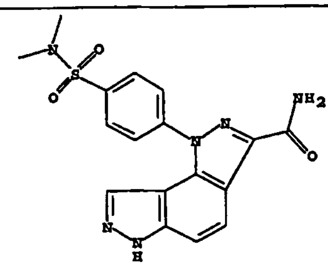
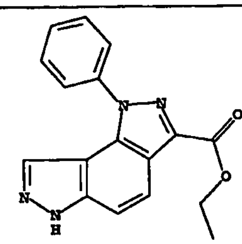
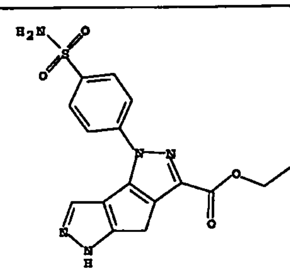
1-[4-(aminocarbonyl)phenyl]-1,4,5,6-tetrahydropyrazolo[3,4-e]indazole-3-carboxamide	
1-(4-methoxyphenyl)-1,4,5,6-tetrahydropyrazolo[3,4-e]indazole-3-carboxamide	
1-[4-(aminosulfonyl)phenyl]-1,6-dihydropyrazolo[3,4-e]indazole-3-carboxamide	
1-{4-[(butylamino)sulfonyl]phenyl}-1,6-dihydropyrazolo[3,4-e]indazole-3-carboxamide	
1-{4-[(methylamino)sulfonyl]phenyl}-1,6-dihydropyrazolo[3,4-e]indazole-3-carboxamide	

TABLE 2 cont

1-{4-[(dimethylamino)sulfonyl]phenyl}-1,6-dihydropyrazolo[3,4-e]indazole-3-carboxamide	
Ethyl 1-phenyl-1,6-dihydropyrazolo[3,4-e]indazole-3-carboxylate	
4-(4-Sulfamoyl-phenyl)-4,7-dihydro-1H-cyclopental[1,2-c;3,4-c']dipyrazole-6-carboxylic acid ethyl ester	

BIOLOGICAL EVALUATION

Materials

[0094] SAM^2 ™ 96 Biotin capture plates were from Promega. Anti-FLAG affinity resin, FLAG-peptide, NP-40 (Nonidet P-40), BSA, ATP, ADP, AMP, LPS (*E. coli* serotype 0111:B4), and dithiothreitol were obtained from Sigma Chemicals. Antibodies specific for NEMO (IKKγ) (FL-419), IKK1(H-744), IKK2(H-470) and IκBα(C-21) were purchased from Santa Cruz Biotechnology. Ni-NTA resin was purchased from Qiagen. Peptides were purchased from American Peptide Company. Protease inhibitor cocktail tablets were from Boehringer Mannheim. Sephacryl S-300 column was from Pharmacia LKB Biotechnology. Centriprep-10 concentrators with a molecular weight cutoff of 10 kDa and membranes with

molecular weight cut-off of 30 kDa were obtained from Amicon. [Υ-^{33}P] ATP (2500 Ci/mmol) and [Υ-^{32}P] ATP (6000 Ci/mmol) were purchased from Amersham. The other reagents used were of the highest grade commercially available.

Cloning and Expression

[0095] cDNAs of human IKK1 and IKK2 were amplified by reverse transcriptase-polymerase chain reaction from human placental RNA (Clonetech). hIKK1 was subcloned into pFastBac HTa (Life Technologies) and expressed as N-terminal His_6-tagged fusion protein. The hIKK2 cDNA was amplified using a reverse oligonucleotide primer which incorporated the peptide sequence for a FLAG-epitope tag at the C-terminus of the IKK2 coding region (DYKDDDDKD). The hIKK2:FLAG cDNA was subcloned into the baculovirus vector pFastBac. The rhIKK2 (S177S, E177E) mutant was constructed in the same vector used for wild type rhIKK2 using a QuikChange™ mutagenesis kit (Stratagene). Viral stocks of each construct were used to infect insect cells grown in 40L suspension culture. The cells were lysed at a time that maximal expression and rhIKK activity were demonstrated. Cell lysates were stored at -80 °C until purification of the recombinant proteins was undertaken as described below.

Enzyme Isolation

[0096] All purification procedures were carried out at 4 °C unless otherwise noted. Buffers used are: buffer A: 20 mM Tris-HCl, pH 7.6, containing 50 mM NaCl, 20 mM NaF, 20 mM β-Glycerophosphate, 500 uM sodiumortho-vanadate, 2.5 mM metabisulfite, 5 mM benzamidine, 1 mM EDTA, 0.5 mM EGTA, 10% glycerol, 1 mM DTT, 1X Complete™ protease inhibitors; buffer B: same as buffer A, except 150 mM NaCl, and buffer C: same as buffer A, except 500 mM NaCl.

Isolation of rhIKK1 homodimer

[0097] Cells from an 8 liter fermentation of baculovirus-expressed IKK1 tagged with His peptide were centrifuged and the cell pellet (MOI 0.1, I=72 hr) was re-suspended in 100 ml of buffer C. The cells were microfluidized and centrifuged at 100,000 X g for 45 min. The supernatant was collected, imidazole added to the

final concentration of 10 mM and incubated with 25 ml of Ni-NTA resin for 2 hrs. The suspension was poured into a 25 ml column and washed with 250 ml of buffer C and then with 125 ml of 50 mM imidazole in buffer C. rhIKK1 homodimer was eluted using 300 mM imidazole in buffer C. BSA and NP-40 were added to the enzyme fractions to the final concentration of 0.1 %. The enzyme was dialyzed against buffer B, aliquoted and stored at -80 °C.

Isolation of rhIKK2 homodimer

[0098] A 10 liter culture of baculovirus-expressing IKK2 tagged with FLAG peptide was centrifuged and the cell pellet (MOI=0.1 and I=72 hrs) was re-suspended in buffer A. These cells were microfluidized, and centrifuged at 100,000 X g for 45 min. Supernatant was passed over a G-25 column equilibrated with Buffer A. Protein peak was collected and incubated with anti-FLAG affinity resin on a rotator overnight in buffer B. The resin was washed in batch with 10-15 bed volumes of buffer C. Washed resin was poured into a column and rhIKK2 homodimer was eluted using 5 bed volumes of buffer B containing FLAG peptide. 5 mM DTT, 0.1% NP-40 and BSA (concentrated to 0.1% in final amount) was added to the eluted enzyme before concentrating in using an Amicon membrane with a molecular weight cut-off of 30 kDa. Enzyme was aliquoted and stored at -80 °C.

Isolation of rhIKK1/IKK2 heterodimer

[0099] The heterodimer enzyme was produced by coinfection in a baculovirus system (FLAG IKK2/IKK1 His; MOI=0.1 and I=72 hrs). Infected cells were centrifuged and the cell pellet (10.0 g) was suspended in 50 ml of buffer A. The protein suspension was microfluidized and centrifuged at 100,000 X g for 45 min. Imidazole was added to the supernatant to a final concentration of 10 mM. The protein was allowed to bind 25 ml of Ni-NTA resin by mixing for 2 hrs. The protein-resin slurry was poured into a 25 ml column and washed with 250 ml of buffer A containing 10 mM imidazole followed by 125 ml of buffer A containing 50 mM imidazole. Buffer A, containing 300 mM imidazole, was then used to elute the protein. A 75 ml pool was collected and NP-40 was added to a final

concentration of 0.1%. The protein solution was then dialyzed against buffer B. The dialyzed heterodimer enzyme was then allowed to bind to 25 ml of anti-FLAG M2 agarose affinity gel overnight with constant mixing. The protein-resin slurry was then centrifuged for 5 min at 2,000 rpm. The supernatant was collected and the resin re-suspended in 100 ml of buffer C containing 0.1% NP-40. The resin was washed with 375 ml of buffer C containing 0.1 % NP-40. The protein-resin was poured into a 25 ml column and the enzyme eluted using buffer B containing FLAG peptide. Enzyme fractions (100 ml) were collected and concentrated to 20 ml using an Amicon membrane with molecular weight cut-off of 30 kDa. Bovine serum albumin was added to the concentrated enzyme to final concentration of 0.1 %. The enzyme was then aliquoted and stored at -80 °C.

Cell Culture

[00100] The wild type (wt) human pre-B cell line, 70Z/3, and its mutant, 1.3E2, were generously provided by Dr. Carol Sibley. Wt 70Z/3 and 1.3E2 cells were grown in RPMI 1640 (Gibco) supplemented with 7 % defined bovine serum (Hyclone) and 50 μM 2-mercaptoethanol. Human monocytic leukemia THP-1 cells, obtained from ATCC, were cultured in RPMI 1640 supplemented with 10% defined bovine serum, 10 mM HEPES, 1.0 mM sodium pyruvate and 50 μM 2-mercaptoethanol. For experiments, cells were plated in 6 well plates at $1x10^6$ cells/ml in fresh media. Pre-B cells were stimulated by the addition of 10 μg/ml LPS for varying lengths of time ranging from 0-4 hr. THP-1 cells were stimulated by the addition of 1 μg/ml LPS for 45 minutes. Cells were pelleted, washed with cold 50 mM sodium phosphate buffer, pH 7.4 containing 0.15 M NaCl and lysed at 4 °C in 20 mM Hepes buffer, pH 7.6 containing 50 mM NaCl, 1 mM EDTA, 1 mM EGTA, 1 mM sodium orthovanadate, 10 mM β-glycerophosphate, 1 mM NaF, 1 mM PMSF, 1 mM DTT and 0.5 % NP40 (lysis buffer). The cytosolic fractions obtained following centrifugation at 10,000 X g were stored at -80° C until used.

Immunoprecipitation and Western Blotting

[00101] SF9 cells paste containing rhIKKs were centrifuged (100,000 X g, 10 min) to remove debris. rhIKKs were immunoprecipitated (100 μg of cell paste) from the cell supernatant using 3 μg of anti-NEMO antibody (FL-419), followed by coupling to protein A sepharose beads. rhIKKs were also immunoprecipitated from affinity chromatography purified protein preparations (1 μg) using anti-FLAG, anti-His or anti-NEMO antibodies (1-4 μg) followed by protein A sepharose coupling. The native, human IKK complex was immunoprecipitated from THP-1 cell homogenates (300 μg/condition) using the anti-NEMO antibody. Immune complexes were pelleted and washed 3 times with 1 ml cold lysis buffer. Immunoprecipitated rhIKKs were chromatographed by SDS-PAGE (8% Tris-glycine) and transferred to nitrocellulose membranes (Novex) and detected by chemiluminescense (SuperSignal) using specific anti-IKK antibodies (IKK2 H-470, IKK1 H-744). Native IKK2, IκBα and NEMO proteins from cytosolic lysates (20-80 μg) were separated by SDS-PAGE and visualized by chemiluminescense using specific antibodies.

Phosphatase Treatment

[00102] Immunoprecipitated rhIKKs were washed 2 times in 50 mM Tris-HCl, pH 8.2 containing 0.1 mM EDTA, 1 mM DTT, 1 mM PMSF and 2 mM $MnCl_2$ and resuspended in 50 μl. Phosphatase (λPPase, 1000 U) was pre-diluted in the same buffer and added to the IKK samples. Following an incubation at room temperature for 30 minutes with intermittent mixing, cold lysis buffer was added to the tubes to stop the reaction. After several washes, 10 % of the beads were removed for Western analysis, and the remaining material was pelleted and resuspended in 100 μl of the buffer used for the *in vitro* kinase assay.

IKKα SAM Enzyme Assay

[00103] IKKα kinase activity was measured using a biotinylated IκBα peptide (Gly-Leu-Lys-Lys-Glu-Arg-Leu-Leu-Asp-Asp-Arg-His-Asp-Ser_{32}-Gly-Leu-Asp-Ser_{36}-Met-Lys-Asp-Glu-Glu), a SAM^{2} ™ 96 Biotin capture plate, and a vacuum

system. The standard reaction mixture contained 5 μM biotinylated IκBα peptide, 1 μM [γ-^{33}P] ATP (about 1 X 10^5 cpm), 1 mM DTT, 50 mM KCl, 2 mM $MgCl_2$, 2 mM $MnCl_2$, 10 mM NaF, 25 mM Hepes buffer, pH. 7.6 and enzyme solution (1-10 μl) in a final volume of 50 μl. After incubation at 25 °C for 30 min, 25 μl of the reaction mixture was withdrawn and added to a SAM^{2} ™ 96 Biotin capture 96-well plate. Each well was then washed successively with 800 μl 2 M NaCl, 1.2 ml of NaCl containing 1% H_3PO_4, 400 μl H_2O, and 200 μl 95% ethanol. The plate was allowed to dry in a hood at 25 °C for 1 hr and then 25 μl of scintillation fluid (Microscint 20) was added to each well. Incorporation of [γ-^{33}P] ATP was measured using a Top-Count NXT (Packard). Under each assay condition, the degree of phosphorylation of IκBα peptide substrate was linear with time and concentration for all purified enzymes. Results from the biotinylated peptide assay were confirmed by SDS-PAGE analysis of kinase reaction utilizing a GST-IκBα_{1-54} and [γ-^{32}P] ATP. The resulting radiolabeled substrate was quantitated by Phosphoimager (Molecular Dynamics). An ion exchange resin assay was also employed using [γ-^{33}P] ATP and GST-IκBα_{1-54} fusion protein as the substrates. Each assay system yielded consistent results in regard to K_m and specific activities for each of the purified kinase isoforms. One unit of enzyme activity was defined as the amount required to catalyze the transfer of 1 nmole of phosphate from ATP to IκBα peptide per min. Specific activity was expressed as units per mg of protein. For experiments related to K_m determination of purified enzymes, various concentrations of ATP or IκBα peptide were used in the assay at either a fixed IκBα or ATP concentration. For IκBα peptide K_m, assays were carried out with 0.1 μg of enzyme, 5 μM ATP and IκBα peptide from 0.5 to 20 μM. For ATP K_m, assays were carried out with 0.1 μg of enzyme, 10 μM IκBα peptide and ATP from 0.1 to 10 μM. For K_m determination of rhIKK1 homodimer, due to its low activity and higher K_m for IκBα peptide, rhIKK1 homodimer (0.3 μg) was assayed with 125 μM IκBα peptide and a 5-fold higher specific activity of ATP (from 0.1 to 10 μM) for ATP K_m experiments and a 5-fold higher specific activity of 5 μM ATP and IκBα peptide (from 5 to 200 μM) for IκBα peptide K_m experiments.

IKKβ Resin Enzyme Assay

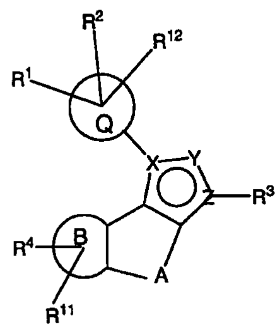
[00104] IKKβ kinase activity was measured using a biotinylated IκBα peptide (Gly-Leu-Lys-Lys-Glu-Arg-Leu-Leu-Asp-Asp-Arg-His-Asp-Ser_{32}-Gly-Leu-Asp-Ser_{36}-Met-Lys-Asp-Glu-Glu) (American Peptide Co.). 20 ul of the standard reaction mixture contained 5 μM biotinylated IκBα peptide, 0.1 μCi/reaction [γ-^{33}P] ATP (Amersham) (about 1 X 10^5 cpm), 1 μM ATP (Sigma), 1 mM DTT (Sigma), 2 mM $MgCl_2$ (Sigma), 2 mM $MnCl_2$ (Sigma), 10 mM NaF (Sigma), 25 mM Hepes (Sigma) buffer, pH 7.6 and 20 μl enzyme solution and 10 ul inhibitor in a final volume of 50 μl. After incubation at 25 °C for 30 min, 150 μl resin (Dowex anion-exchange resin AG1X8 200-400 mesh) in 900 mM formate, pH 3.0 was added to each well to stop the reaction. Resin was allowed to settle for one hour and 50 ul of supernatant was removed to a Micolite-2 flat bottom plate (Dynex). 150 μl of scintillation fluid (Microscint 40) (Packard) was added to each well. Incorporation of [γ-^{33}P] ATP was measured using a Top-Count NXT (Packard).

IKK heterodimer Resin Enzyme Assay

[00105] IKK heterodimer kinase activity was measured using a biotinylated IκBα peptide (Gly-Leu-Lys-Lys-Glu-Arg-Leu-Leu-Asp-Asp-Arg-His-Asp-Ser_{32}-Gly-Leu-Asp-Ser_{36}-Met-Lys-Asp-Glu-Glu) (American Peptide Co.). 20 ul of the standard reaction mixture contained 5 μM biotinylated IκBα peptide, 0.1 μCi/reaction [γ-^{33}P] ATP (Amersham) (about 1 X 10^5 cpm), 1 μM ATP (Sigma), 1 mM DTT (Sigma), 2 mM $MgCl_2$ (Sigma), 2 mM $MnCl_2$ (Sigma), 10 mM NaF (Sigma), 25 mM Hepes (Sigma) buffer, pH 7.6 and 20 μl enzyme solution and 10 μl inhibitor in a final volume of 50 μl. After incubation at 25 °C for 30 min, 150 μl resin (Dowex anion-exchange resin AG1X8 200-400 mesh) in 900 mM formate, pH 3.0 was added to each well to stop the reaction. Resin was allowed to settle for one hour and 50 ul of supernatant was removed to a Micolite-2 flat bottom plate (Dynex). 150 μl of scintillation fluid (Microscint 40) (Packard) was added to each well. Incorporation of [γ-^{33}P] ATP was measured using a Top-Count NXT (Packard).

What is claimed is:

1. A compound of formula I



wherein

A is $(CH_2)_m$; wherein each CH_2 may be independently substituted with one or more substitution selected from the group consisting of: hydroxy, halo, alkoxy, lower alkyl, amino, aminoalkyl, alkylamino, alkenyl, and alkynyl;

m is 0 to 8;

Q is a 5 or 6 membered heteroaryl, or aryl, optionally saturated, or optionally substituted with R^1, R^2, or R^{12};

B is an aromatic heterocyclic;

X is selected from the group consisting of: N and C;

Y and **Z** are independently selected from the group consisting of: N, C, CH, CR^3, S, and O;

$\mathbf{R^1}$ is selected from the group consisting of: hydrido, halogen, alkyl, aryl, heteroaryl, alkenyl, alkynyl, haloalkyl, CN, NO_2, OR^5, $OCOOR^5$, CO_2R^7, $CON(R^6)R^7$, COR^6, SR^6, SOR^6, SO_2R^6, NR^6R^7, NR^6COR^7, NR^6CONHR^7, $NR^6SO_2R^7$, $NR^6SO_2NHR^7$, and $SO_2N(R^6)R^7$ wherein R^6 and R^7 may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from the group consisting of: S, SO, SO_2, O, and NR^6; wherein said alkenyl, alkynyl, alkyl, aryl, heteroaryl or OR^5

are optional substituted with, hydrido, halogen, alkyl, hydroxyalkyl, aryl, heteroaryl, haloalkyl, $COCF_3$, CN, NO_2, OR^5, $OCOOR^5$, CO_2R^7, $CON(R^6)R^7$, COR^6, SR^6, SOR^6, SO_2R^6, NR^6R^7, NR^6COR^7, NR^6CONHR^7, $NR^6SO_2R^7$, $NR^6SO_2NHR^7$, and $SO_2N(R^6)R^7$ wherein R^6 and R^7 may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from the group consisting of: S, SO, SO_2, O, and NR^6;

R^2 is selected from the group consisting of: halogen, hydrido, hydroxyalkyl, alkyl, OR^6, CN, NO_2, SR^6, NHR^6, $CON(R^6)R^7$, $NHCONHR^6$, CO_2H, and haloalkyl;

R^1 and **R^2** may be taken together to form a 5 to 7 membered saturated or unsaturated carbocyclic ring optionally containing 0 to 3 heteroatoms selected from the group consisting of: N, O, or S, and wherein said ring is optionally substituted with R^1;

R^3 is selected from the group consisting of: substituted or unsubstituted amidine, alkylamino, aminoalkyl, $CONHR^{16}$, NH_2, $NHCOR^6$, and CH_2NHCOR^6;

R^4 is selected from the group consisting of: halogen, alkylsulfinyl, alkylsulfonyl, cyano, alkoxycarbonyl, alkyl, haloalkyl, hydrido, hydroxyalkyl, haloalkoxy, heterocyclic, nitro, acylamino, aryl, heteroaryl, and alkenyl, OR^{13}, SR^8, $SO_2N(R^8)R^{8'}$, NHR^9, $NHCOR^9$, NR^9COR^9, $NHCO(OR^9)$, $NR^9CO(OR^9)$, $NR^8SO_2R^{10}$, $NHSO_2N(R^{10})R^{10'}$, $NR^6CON(R^{10})R^{10'}$, COR^9, CO_2R^8, $CON(R^8)R^{8'}$, wherein R^8 and $R^{8'}$ may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from S, SO, SO_2, O, N, and NR^6, and wherein R^{10} and $R^{10'}$ may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from S, SO, SO_2, O, N, and NR^6 wherein said aryl, heterocyclic, heteroaryl, or alkenyl are optionally substituted with R^9;

$\mathbf{R^5}$ is selected from the group consisting of: hydrido, alkyl, aryl, arylalkyl, heteroaryl, heterocyclicalkyl, and heteroarylalkyl, wherein aryl, alkyl, arylalkyl, heteroaryl, heterocyclicalkyl, or heteroarylalkyl are optionally substituted with one or more radicals selected from the group consisting of: OR^{14}, $N(R^{14})R^{14'}$, and glycols;

$\mathbf{R^6}$ is independently selected from the group consisting of: hydrido, aryl, heteroaryl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, heterocyclicalkyl, and heterocyclic;

$\mathbf{R^7}$ is independently selected from the group consisting of: hydrido, aryl, heteroaryl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, heterocyclicalkyl, and heterocyclic;

$\mathbf{R^8}$ is independently selected from the group consisting of: hydrido, aryl, heteroaryl, arylalkyl, heterocyclic, haloalkyl, arylalkylamino, alkylaminoalkyl, dialkylaminoalkyl, alkyl, alkenyl, alkynyl, heteroarylalkyl, and heterocyclicalkyl;

$\mathbf{R^{8'}}$ is independently selected from the group consisting of: hydrido, aryl, heteroaryl, arylalkyl, heterocyclic, haloalkyl, arylalkylamino, alkylaminoalkyl, dialkylaminoalkyl, alkyl, alkenyl, alkynyl, heteroarylalkyl, and heterocyclicalkyl;

$\mathbf{R^9}$ is independently selected from the group consisting of: hydrido, lower alkyl, aryl, heteroaryl, arylalkyl, heterocyclic, cycloalkyl, heterocyclicalkyl, haloalkyl, arylalkylamino, amino, aminoalkyl, aminoacyl, nitro, azido, and heteroarylalkyl, wherein alkyl, aryl, heteroaryl, aminoalkyl, or arylalkyl are optionally substituted with one or more radical selected from the group consisting of: alkylsulfonamide, sulfamyl, alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, aminoalkyl, alkylaminoalkyl, alkoxy, halogen, acyloxy, oxy, formyl, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, nitro, azido, benzyloxy, dialkylaminoacyl, thioalkyl, aminoacyloxy, thiocyanate,

isothiocyanate, alkyldioxy, hydroxyalkyl, alkylamino, alkyloxycarbonyl, alkoxyalkyl, alkenylamino, alkynylamino, alkenyl, alkynyl, dialkylaminoalkyloxy, and heterocyclic optionally substituted with alkyl, alkylamino, aminoalkyl, hydroxyalkyl, and alkylaminoalkyl;

R^{10} is independently selected from the group consisting of: hydrido, lower alkyl, heteroaryl, heterocyclic, haloalkyl, arylalkylamino, heteroarylalkyl, aryl, and arylalkyl, wherein aryl, heteroaryl, heterocyclic, or arylalkyl are optionally substituted with one or more radical selected from alkyl, alkoxy, halogen, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, benzyloxy, dialkylaminoalkyloxy, and heterocyclic,

$R^{10'}$ is independently selected from the group consisting of: hydrido, lower alkyl, heteroaryl, heterocyclic, haloalkyl, arylalkylamino, heteroarylalkyl, aryl, and arylalkyl, wherein aryl, heteroaryl, heterocyclic, or arylalkyl are optionally substituted with one or more radical selected from alkyl, alkoxy, halogen, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, benzyloxy, dialkylaminoalkyloxy, and heterocyclic,

R^{11} is selected from the group consisting of: hydrido, halogen, haloalkyl, CN, CO_2R^5, lower alkyl, lower alkenyl, lower alkynyl, alkoxy, and $CONH_2$;

R^{12} is selected from the group consisting of: hydrido, halogen, alkyl, and alkoxy;

R^{13} is selected from the group consisting of: hydrido, alkyl, aryl, arylalkyl, heteroaryl, heterocyclicalkyl, and heteroarylalkyl, wherein aryl, alkyl, arylalkyl, heteroaryl, heterocyclicalkyl, or heteroarylalkyl are optionally substituted with one or more radicals selected from the group consisting of: OR^{14}, $N(R^{14})R^{14'}$, and glycols;

R^{14} is independently selected from the group consisting of: hydrido, and lower alkyl;

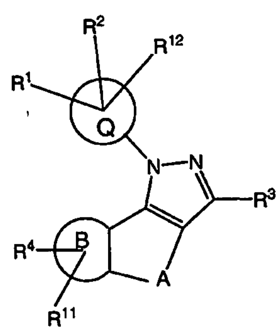
R$^{14'}$ is independently selected from the group consisting of: hydrido, and lower alkyl;

R^{15} is selected from the group consisting of: hydrido, halogen, alkyl, cycloalkyl, aryl, haloalkyl, heteroaryl, heterocyclic, alkylalkene, alkylalkyne, hydroxy, hydroxyalkyl, alkylhydroxy, amino, aminoalkyl, alkylamino, alkylaminoalkyl, alkylhydroxyalkyl, nitro, cyano, alkylthio, alkylsulfinyl, and alkylsulfonyl; wherein aryl or arylalkyl are optionally substituted with one or more radical selected from alkyl, alkoxy, halo, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, benzyloxy, dialkylaminoalkyloxy, heterocyclic; and

R^{16} is independently selected from the group consisting of: hydrido, aryl, arylalkyl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkoxy, and alkoxyalkyl;

or isomers, tautomers, carriers, esters, prodrugs, pharmaceutically acceptable salts thereof.

2. A compound of formula II



wherein

A is $(CH_2)_m$; wherein each CH_2 may be independently substituted with one or more substitution selected from the group consisting of:

hydroxy, halo, alkoxy, lower alkyl, amino, aminoalkyl, alkylamino, alkenyl, and alkynyl;

m is 0 to 8;

Q is a 5 or 6 membered heteroaryl, or aryl, optionally saturated, or optionally substituted with R^1, R^2, or R^{12};

B is an aromatic heterocyclic;

$\mathbf{R^1}$ is selected from the group consisting of: hydrido, halogen, alkyl, aryl, heteroaryl, alkenyl, alkynyl, haloalkyl, CN, NO_2, OR^5, $OCOOR^5$, CO_2R^7, $CON(R^6)R^7$, COR^6, SR^6, SOR^6, SO_2R^6, NR^6R^7, NR^6COR^7, NR^6CONHR^7, $NR^6SO_2R^7$, $NR^6SO_2NHR^7$, and $SO_2N(R^6)R^7$ wherein R^6 and R^7 may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from the group consisting of: S, SO, SO_2, O, and NR^6; wherein said alkenyl, alkynyl, alkyl, aryl, heteroaryl or OR^5 are optional substituted with, hydrido, halogen, alkyl, hydroxyalkyl, aryl, heteroaryl, haloalkyl, $COCF_3$, CN, NO_2, OR^5, $OCOOR^5$, CO_2R^7, $CON(R^6)R^7$, COR^6, SR^6, SOR^6, SO_2R^6, NR^6R^7, NR^6COR^7, NR^6CONHR^7, $NR^6SO_2R^7$, $NR^6SO_2NHR^7$, and $SO_2N(R^6)R^7$ wherein R^6 and R^7 may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from the group consisting of: S, SO, SO_2, O, and NR^6;

$\mathbf{R^2}$ is selected from the group consisting of: halogen, hydrido, hydroxyalkyl, alkyl, OR^6, CN, NO_2, SR^6, NHR^6, $CON(R^6)R^7$, $NHCONHR^6$, CO_2H, and haloalkyl;

$\mathbf{R^1}$ and $\mathbf{R^2}$ may be taken together to form a 5 to 7 membered saturated or unsaturated carbocyclic ring optionally containing 0 to 3 heteroatoms selected from the group consisting of: N, O, or S, and wherein said ring is optionally substituted with R^1;

$\mathbf{R^3}$ is selected from the group consisting of: substituted or unsubstituted amidine, alkylamino, aminoalkyl, $CONHR^{16}$, NH_2, $NHCOR^6$, and CH_2NHCOR^6;

R^4 is selected from the group consisting of: halogen, alkylsulfinyl, alkylsulfonyl, cyano, alkoxycarbonyl, alkyl, haloalkyl, hydrido, hydroxyalkyl, haloalkoxy, heterocyclic, nitro, acylamino, aryl, heteroaryl, and alkenyl, OR^{13}, SR^8, $SO_2N(R^8)R^{8'}$, NHR^9, $NHCOR^9$, NR^9COR^9, $NHCO(OR^9)$, $NR^9CO(OR^9)$, $NR^8SO_2R^{10}$, $NHSO_2N(R^{10})R^{10'}$, $NR^6CON(R^{10})R^{10'}$, COR^9, CO_2R^8, $CON(R^8)R^{8'}$, wherein R^8 and $R^{8'}$ may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from S, SO, SO_2, O, N, and NR^6, and wherein R^{10} and $R^{10'}$ may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from S, SO, SO_2, O, N, and NR^6 wherein said aryl, heterocyclic, heteroaryl, or alkenyl are optionally substituted with R^9;

R^5 is selected from the group consisting of: hydrido, alkyl, aryl, arylalkyl, heteroaryl, heterocyclicalkyl, and heteroarylalkyl, wherein aryl, alkyl, arylalkyl, heteroaryl, heterocyclicalkyl, or heteroarylalkyl are optionally substituted with one or more radicals selected from the group consisting of: OR^{14}, $N(R^{14})R^{14'}$, and glycols;

R^6 is independently selected from the group consisting of: hydrido, aryl, heteroaryl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, heterocyclicalkyl, and heterocyclic;

R^7 is independently selected from the group consisting of: hydrido, aryl, heteroaryl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, heterocyclicalkyl, and heterocyclic;

R^8 is independently selected from the group consisting of: hydrido, aryl, heteroaryl, arylalkyl, heterocyclic, haloalkyl, arylalkylamino, alkylaminoalkyl, dialkylaminoalkyl, alkyl, alkenyl, alkynyl, heteroarylalkyl, and heterocyclicalkyl;

$R^{8'}$ is independently selected from the group consisting of: hydrido, aryl, heteroaryl, arylalkyl, heterocyclic, haloalkyl, arylalkylamino, alkylaminoalkyl, dialkylaminoalkyl, alkyl, alkenyl, alkynyl, heteroarylalkyl, and heterocyclicalkyl;

R^9 is independently selected from the group consisting of: hydrido, lower alkyl, aryl, heteroaryl, arylalkyl, heterocyclic, cycloalkyl, heterocyclicalkyl, haloalkyl, arylalkylamino, amino, aminoalkyl, aminoacyl, nitro, azido, and heteroarylalkyl, wherein alkyl, aryl, heteroaryl, aminoalkyl, or arylalkyl are optionally substituted with one or more radical selected from the group consisting of: alkylsulfonamide, sulfamyl, alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, aminoalkyl, alkylaminoalkyl, alkoxy, halogen, acyloxy, oxy, formyl, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, nitro, azido, benzyloxy, dialkylaminoacyl, thioalkyl, aminoacyloxy, thiocyanate, isothiocyanate, alkyldioxy, hydroxyalkyl, alkylamino, alkyloxycarbonyl, alkoxyalkyl, alkenylamino, alkynylamino, alkenyl, alkynyl, dialkylaminoalkyloxy, and heterocyclic optionally substituted with alkyl, alkylamino, aminoalkyl, hydroxyalkyl, and alkylaminoalkyl;

R^{10} is independently selected from the group consisting of: hydrido, lower alkyl, heteroaryl, heterocyclic, haloalkyl, arylalkylamino, heteroarylalkyl, aryl, and arylalkyl, wherein aryl, heteroaryl, heterocyclic, or arylalkyl are optionally substituted with one or more radical selected from alkyl, alkoxy, halogen, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, benzyloxy, dialkylaminoalkyloxy, and heterocyclic,

$R^{10'}$ is independently selected from the group consisting of: hydrido, lower alkyl, heteroaryl, heterocyclic, haloalkyl, arylalkylamino, heteroarylalkyl, aryl, and arylalkyl, wherein aryl, heteroaryl, heterocyclic, or arylalkyl are optionally substituted with one or more radical selected from alkyl, alkoxy, halogen, haloalkyl, cyano,

haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, benzyloxy, dialkylaminoalkyloxy, and heterocyclic,

R^{11} is selected from the group consisting of: hydrido, halogen, haloalkyl, CN, CO_2R^5, lower alkyl, lower alkenyl, lower alkynyl, alkoxy, and $CONH_2$;

R^{12} is selected from the group consisting of: hydrido, halogen, alkyl, and alkoxy;

R^{13} is selected from the group consisting of: hydrido, alkyl, aryl, arylalkyl, heteroaryl, heterocyclicalkyl, and heteroarylalkyl, wherein aryl, alkyl, arylalkyl, heteroaryl, heterocyclicalkyl, or heteroarylalkyl are optionally substituted with one or more radicals selected from the group consisting of: OR^{14}, $N(R^{14})R^{14'}$, and glycols;

R^{14} is independently selected from the group consisting of: hydrido, and lower alkyl;

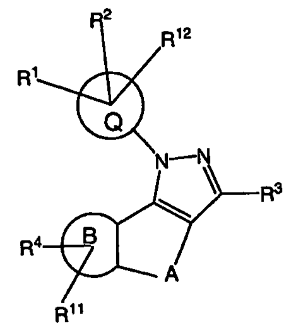
$R^{14'}$ is independently selected from the group consisting of: hydrido, and lower alkyl;

R^{15} is selected from the group consisting of: hydrido, halogen, alkyl, cycloalkyl, aryl, haloalkyl, heteroaryl, heterocyclic, alkylalkene, alkylalkyne, hydroxy, hydroxyalkyl, alkylhydroxy, amino, aminoalkyl, alkylamino, alkylaminoalkyl, alkylhydroxyalkyl, nitro, cyano, alkylthio, alkylsulfinyl, and alkylsulfonyl; wherein aryl or arylalkyl are optionally substituted with one or more radical selected from alkyl, alkoxy, halo, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, benzyloxy, dialkylaminoalkyloxy, heterocyclic; and

R^{16} is independently selected from the group consisting of: hydrido, aryl, arylalkyl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkoxy, and alkoxyalkyl;

or isomers, tautomers, carriers, esters, prodrugs, pharmaceutically acceptable salts thereof.

3. The compound of claim 2



wherein

A is $(CH_2)_m$; wherein each CH_2 may be independently substituted with one or more substitution selected from the group consisting of: hydroxy, halo, alkoxy, lower alkyl, amino, aminoalkyl, alkylamino, alkenyl, and alkynyl;

m is 0 to 8;

Q is a 5 or 6 membered heteroaryl, or aryl, optionally saturated, or optionally substituted with R^1, R^2, or R^{12};

B is an aromatic heterocyclic;

$\mathbf{R^1}$ is selected from the group consisting of: hydrido, halogen, alkyl, aryl, heteroaryl, alkenyl, alkynyl, haloalkyl, CN, NO_2, OR^5, $OCOOR^5$, CO_2R^7, $CON(R^6)R^7$, COR^6, SR^6, SOR^6, SO_2R^6, NR^6R^7, NR^6COR^7, NR^6CONHR^7, $NR^6SO_2R^7$, $NR^6SO_2NHR^7$, and $SO_2N(R^6)R^7$ wherein R^6 and R^7 may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from the group consisting of: S, SO, SO_2, O, and NR^6; wherein said alkenyl, alkynyl, alkyl, aryl, heteroaryl or OR^5 are optional substituted with, hydrido, halogen, alkyl, hydroxyalkyl, aryl, heteroaryl, haloalkyl, $COCF_3$, CN, NO_2, OR^5, $OCOOR^5$, CO_2R^7, $CON(R^6)R^7$, COR^6, SR^6, SOR^6, SO_2R^6, NR^6R^7, NR^6COR^7, NR^6CONHR^7, $NR^6SO_2R^7$, $NR^6SO_2NHR^7$, and $SO_2N(R^6)R^7$ wherein R^6 and R^7 may be taken together to form a 3-7 membered

carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from the group consisting of: S, SO, SO_2, O, and NR^6;

R^2 is selected from the group consisting of: halogen, hydrido, hydroxyalkyl, alkyl, OR^6, CN, NO_2, SR^6, NHR^6, $CON(R^6)R^7$, $NHCONHR^6$, CO_2H, and haloalkyl;

R^1 and **R^2** may be taken together to form a 5 to 7 membered saturated or unsaturated carbocyclic ring optionally containing 0 to 3 heteroatoms selected from the group consisting of: N, O, or S, and wherein said ring is optionally substituted with R^1;

R^3 is $CONHR^{16}$;

R^4 is selected from the group consisting of: halogen, alkylsulfinyl, alkylsulfonyl, cyano, alkoxycarbonyl, alkyl, haloalkyl, hydrido, hydroxyalkyl, haloalkoxy, heterocyclic, nitro, acylamino, aryl, heteroaryl, and alkenyl, OR^{13}, SR^8, $SO_2N(R^8)R^{8'}$, NHR^9, $NHCOR^9$, NR^9COR^9, $NHCO(OR^9)$, $NR^9CO(OR^9)$, $NR^8SO_2R^{10}$, $NHSO_2N(R^{10})R^{10'}$, $NR^6CON(R^{10})R^{10'}$, COR^9, CO_2R^8, $CON(R^8)R^{8'}$, wherein R^8 and $R^{8'}$ may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from S, SO, SO_2, O, N, and NR^6, and wherein R^{10} and $R^{10'}$ may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from S, SO, SO_2, O, N, and NR^6 wherein said aryl, heterocyclic, heteroaryl, or alkenyl are optionally substituted with R^9;

R^5 is selected from the group consisting of: hydrido, alkyl, aryl, arylalkyl, heteroaryl, heterocyclicalkyl, and heteroarylalkyl, wherein aryl, alkyl, arylalkyl, heteroaryl, heterocyclicalkyl, or heteroarylalkyl are optionally substituted with one or more radicals selected from the group consisting of: OR^{14}, $N(R^{14})R^{14'}$, and glycols;

R^6 is independently selected from the group consisting of: hydrido, aryl, heteroaryl, lower alkyl, haloalkyl, alkenyl, alkynyl,

hydroxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, heterocyclicalkyl, and heterocyclic;

R^7 is independently selected from the group consisting of: hydrido, aryl, heteroaryl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, heterocyclicalkyl, and heterocyclic;

R^8 is independently selected from the group consisting of: hydrido, aryl, heteroaryl, arylalkyl, heterocyclic, haloalkyl, arylalkylamino, alkylaminoalkyl, dialkylaminoalkyl, alkyl, alkenyl, alkynyl, heteroarylalkyl, and heterocyclicalkyl;

R$^{8'}$ is independently selected from the group consisting of: hydrido, aryl, heteroaryl, arylalkyl, heterocyclic, haloalkyl, arylalkylamino, alkylaminoalkyl, dialkylaminoalkyl, alkyl, alkenyl, alkynyl, heteroarylalkyl, and heterocyclicalkyl;

R^9 is independently selected from the group consisting of: hydrido, lower alkyl, aryl, heteroaryl, arylalkyl, heterocyclic, cycloalkyl, heterocyclicalkyl, haloalkyl, arylalkylamino, amino, aminoalkyl, aminoacyl, nitro, azido, and heteroarylalkyl, wherein alkyl, aryl, heteroaryl, aminoalkyl, or arylalkyl are optionally substituted with one or more radical selected from the group consisting of: alkylsulfonamide, sulfamyl, alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, aminoalkyl, alkylaminoalkyl, alkoxy, halogen, acyloxy, oxy, formyl, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, nitro, azido, benzyloxy, dialkylaminoacyl, thioalkyl, aminoacyloxy, thiocyanate, isothiocyanate, alkyldioxy, hydroxyalkyl, alkylamino, alkyloxycarbonyl, alkoxyalkyl, alkenylamino, alkynylamino, alkenyl, alkynyl, dialkylaminoalkyloxy, and heterocyclic optionally substituted with alkyl, alkylamino, aminoalkyl, hydroxyalkyl, and alkylaminoalkyl;

R^{10} is independently selected from the group consisting of: hydrido, lower alkyl, heteroaryl, heterocyclic, haloalkyl, arylalkylamino,

heteroarylalkyl, aryl, and arylalkyl, wherein aryl, heteroaryl, heterocyclic, or arylalkyl are optionally substituted with one or more radical selected from alkyl, alkoxy, halogen, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, benzyloxy, dialkylaminoalkyloxy, and heterocyclic,

$R^{10'}$ is independently selected from the group consisting of: hydrido, lower alkyl, heteroaryl, heterocyclic, haloalkyl, arylalkylamino, heteroarylalkyl, aryl, and arylalkyl, wherein aryl, heteroaryl, heterocyclic, or arylalkyl are optionally substituted with one or more radical selected from alkyl, alkoxy, halogen, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, benzyloxy, dialkylaminoalkyloxy, and heterocyclic,

R^{11} is selected from the group consisting of: hydrido, halogen, haloalkyl, CN, CO_2R^5, lower alkyl, lower alkenyl, lower alkynyl, alkoxy, and $CONH_2$;

R^{12} is selected from the group consisting of: hydrido, halogen, alkyl, and alkoxy;

R^{13} is selected from the group consisting of: hydrido, alkyl, aryl, arylalkyl, heteroaryl, heterocyclicalkyl, and heteroarylalkyl, wherein aryl, alkyl, arylalkyl, heteroaryl, heterocyclicalkyl, or heteroarylalkyl are optionally substituted with one or more radicals selected from the group consisting of: OR^{14}, $N(R^{14})R^{14'}$, and glycols;

R^{14} is independently selected from the group consisting of: hydrido, and lower alkyl;

$R^{14'}$ is independently selected from the group consisting of: hydrido, and lower alkyl;

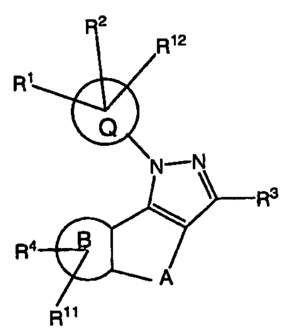
R^{15} is selected from the group consisting of: hydrido, halogen, alkyl, cycloalkyl, aryl, haloalkyl, heteroaryl, heterocyclic, alkylalkene, alkylalkyne, hydroxy, hydroxyalkyl, alkylhydroxy, amino, aminoalkyl, alkylamino, alkylaminoalkyl, alkylhydroxyalkyl, nitro, cyano, alkylthio, alkylsulfinyl, and alkylsulfonyl; wherein aryl or arylalkyl are optionally substituted with one or more radical selected

from alkyl, alkoxy, halo, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, benzyloxy, dialkylaminoalkyloxy, heterocyclic; and

R^{16} is independently selected from the group consisting of: hydrido, aryl, arylalkyl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkoxy, and alkoxyalkyl;

or isomers, tautomers, carriers, esters, prodrugs, pharmaceutically acceptable salts thereof.

4. The compound of claim 3



wherein

A is $(CH_2)_m$; wherein each CH_2 may be independently substituted with one or more substitution selected from the group consisting of: hydroxy, halo, alkoxy, lower alkyl, amino, aminoalkyl, alkylamino, alkenyl, and alkynyl;

m is 0 to 8;

Q is a 5 or 6 membered heteroaryl, or aryl, optionally saturated, or optionally substituted with R^1, R^2, or R^{12};

B is an aromatic heterocyclic;

R^1 is selected from the group consisting of: hydrido, halogen, alkyl, aryl, heteroaryl, alkenyl, alkynyl, haloalkyl, CN, NO_2, OR^5, $OCOOR^5$, CO_2R^7, $CON(R^6)R^7$, COR^6, SR^6, SOR^6, SO_2R^6, NR^6R^7,

NR^6COR^7, NR^6CONHR^7, $NR^6SO_2R^7$, $NR^6SO_2NHR^7$, and $SO_2N(R^6)R^7$ wherein R^6 and R^7 may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from the group consisting of: S, SO, SO_2, O, and NR^6; wherein said alkenyl, alkynyl, alkyl, aryl, heteroaryl or OR^5 are optional substituted with, hydrido, halogen, alkyl, hydroxyalkyl, aryl, heteroaryl, haloalkyl, $COCF_3$, CN, NO_2, OR^5, $OCOOR^5$, CO_2R^7, $CON(R^6)R^7$, COR^6, SR^6, SOR^6, SO_2R^6, NR^6R^7, NR^6COR^7, NR^6CONHR^7, $NR^6SO_2R^7$, $NR^6SO_2NHR^7$, and $SO_2N(R^6)R^7$ wherein R^6 and R^7 may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from the group consisting of: S, SO, SO_2, O, and NR^6;

R^2 is selected from the group consisting of: halogen, hydrido, hydroxyalkyl, alkyl, OR^6, CN, NO_2, SR^6, NHR^6, $CON(R^6)R^7$, $NHCONHR^6$, CO_2H, and haloalkyl;

R^1 and **R^2** may be taken together to form a 5 to 7 membered saturated or unsaturated carbocyclic ring optionally containing 0 to 3 heteroatoms selected from the group consisting of: N, O, or S, and wherein said ring is optionally substituted with R^1;

R^3 is $CONHR^{16}$;

R^4 is selected from the group consisting of: halogen, alkylsulfinyl, alkylsulfonyl, cyano, alkoxycarbonyl, alkyl, haloalkyl, hydrido, hydroxyalkyl, haloalkoxy, heterocyclic, nitro, acylamino, aryl, heteroaryl, and alkenyl, OR^{13}, SR^8, $SO_2N(R^8)R^{8'}$, NHR^9, $NHCOR^9$, NR^9COR^9, $NHCO(OR^9)$, $NR^9CO(OR^9)$, $NR^8SO_2R^{10}$, $NHSO_2N(R^{10})R^{10'}$, $NR^6CON(R^{10})R^{10'}$, COR^9, CO_2R^8, $CON(R^8)R^{8'}$, wherein R^8 and $R^{8'}$ may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from S, SO, SO_2, O, N, and NR^6, and wherein R^{10} and $R^{10'}$ may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted

heteroatoms selected from S, SO, SO_2, O, N, and NR^6 wherein said aryl, heterocyclic, heteroaryl, or alkenyl are optionally substituted with R^9;

R^5 is selected from the group consisting of: hydrido, alkyl, aryl, arylalkyl, heteroaryl, heterocyclicalkyl, and heteroarylalkyl, wherein aryl, alkyl, arylalkyl, heteroaryl, heterocyclicalkyl, or heteroarylalkyl are optionally substituted with one or more radicals selected from the group consisting of: OR^{14}, $N(R^{14})R^{14'}$, and glycols;

R^6 is independently selected from the group consisting of: hydrido, aryl, heteroaryl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, heterocyclicalkyl, and heterocyclic;

R^7 is independently selected from the group consisting of: hydrido, aryl, heteroaryl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, heterocyclicalkyl, and heterocyclic;

R^8 is independently selected from the group consisting of: hydrido, aryl, heteroaryl, arylalkyl, heterocyclic, haloalkyl, arylalkylamino, alkylaminoalkyl, dialkylaminoalkyl, alkyl, alkenyl, alkynyl, heteroarylalkyl, and heterocyclicalkyl;

$R^{8'}$ is independently selected from the group consisting of: hydrido, aryl, heteroaryl, arylalkyl, heterocyclic, haloalkyl, arylalkylamino, alkylaminoalkyl, dialkylaminoalkyl, alkyl, alkenyl, alkynyl, heteroarylalkyl, and heterocyclicalkyl;

R^9 is independently selected from the group consisting of: hydrido, lower alkyl, aryl, heteroaryl, arylalkyl, heterocyclic, cycloalkyl, heterocyclicalkyl, haloalkyl, arylalkylamino, amino, aminoalkyl, aminoacyl, nitro, azido, and heteroarylalkyl, wherein alkyl, aryl, heteroaryl, aminoalkyl, or arylalkyl are optionally substituted with one or more radical selected from the group consisting of: alkylsulfonamide, sulfamyl, alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, aminoalkyl, alkylaminoalkyl, alkoxy,

halogen, acyloxy, oxy, formyl, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, nitro, azido, benzyloxy, dialkylaminoacyl, thioalkyl, aminoacyloxy, thiocyanate, isothiocyanate, alkyldioxy, hydroxyalkyl, alkylamino, alkyloxycarbonyl, alkoxyalkyl, alkenylamino, alkynylamino, alkenyl, alkynyl, dialkylaminoalkyloxy, and heterocyclic optionally substituted with alkyl, alkylamino, aminoalkyl, hydroxyalkyl, and alkylaminoalkyl;

R^{10} is independently selected from the group consisting of: hydrido, lower alkyl, heteroaryl, heterocyclic, haloalkyl, arylalkylamino, heteroarylalkyl, aryl, and arylalkyl, wherein aryl, heteroaryl, heterocyclic, or arylalkyl are optionally substituted with one or more radical selected from alkyl, alkoxy, halogen, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, benzyloxy, dialkylaminoalkyloxy, and heterocyclic,

$R^{10'}$ is independently selected from the group consisting of: hydrido, lower alkyl, heteroaryl, heterocyclic, haloalkyl, arylalkylamino, heteroarylalkyl, aryl, and arylalkyl, wherein aryl, heteroaryl, heterocyclic, or arylalkyl are optionally substituted with one or more radical selected from alkyl, alkoxy, halogen, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, benzyloxy, dialkylaminoalkyloxy, and heterocyclic,

R^{11} is selected from the group consisting of: hydrido, halogen, haloalkyl, CN, CO_2R^5, lower alkyl, lower alkenyl, lower alkynyl, alkoxy, and $CONH_2$;

R^{12} is hydrido;

R^{13} is selected from the group consisting of: hydrido, alkyl, aryl, arylalkyl, heteroaryl, heterocyclicalkyl, and heteroarylalkyl, wherein aryl, alkyl, arylalkyl, heteroaryl, heterocyclicalkyl, or heteroarylalkyl are optionally substituted with one or more radicals selected from the group consisting of: OR^{14}, $N(R^{14})R^{14'}$, and glycols;

R^{14} is independently selected from the group consisting of: hydrido, and lower alkyl;

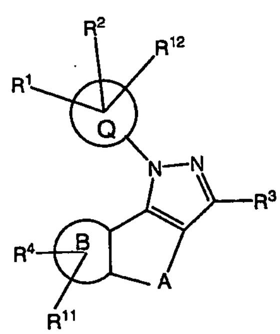
R$^{14'}$ is independently selected from the group consisting of: hydrido, and lower alkyl;

R^{15} is selected from the group consisting of: hydrido, halogen, alkyl, cycloalkyl, aryl, haloalkyl, heteroaryl, heterocyclic, alkylalkene, alkylalkyne, hydroxy, hydroxyalkyl, alkylhydroxy, amino, aminoalkyl, alkylamino, alkylaminoalkyl, alkylhydroxyalkyl, nitro, cyano, alkylthio, alkylsulfinyl, and alkylsulfonyl; wherein aryl or arylalkyl are optionally substituted with one or more radical selected from alkyl, alkoxy, halo, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, benzyloxy, dialkylaminoalkyloxy, heterocyclic; and

R^{16} is independently selected from the group consisting of: hydrido, aryl, arylalkyl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkoxy, and alkoxyalkyl;

or isomers, tautomers, carriers, esters, prodrugs, pharmaceutically acceptable salts thereof.

5. The compound of claim 3



wherein

A is $(CH_2)_m$; wherein each CH_2 may be independently substituted with one or more substitution selected from the group consisting of: hydroxy, halo, alkoxy, lower alkyl, amino, aminoalkyl, alkylamino, alkenyl, and alkynyl;

m is 0 to 8;

n is independently selected from 0, 1, or 2;

Q is a 5 or 6 membered heteroaryl, or aryl, optionally saturated, or optionally substituted with R^1, R^2, or R^{12};

B is an aromatic heterocyclic;

$\mathbf{R^1}$ is selected from the group consisting of: hydrido, halogen, alkyl, aryl, heteroaryl, alkenyl, alkynyl, haloalkyl, CN, NO_2, OR^5, $OCOOR^5$, CO_2R^7, $CON(R^6)R^7$, COR^6, SR^6, SOR^6, SO_2R^6, NR^6R^7, NR^6COR^7, NR^6CONHR^7, $NR^6SO_2R^7$, $NR^6SO_2NHR^7$, and $SO_2N(R^6)R^7$ wherein R^6 and R^7 may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from the group consisting of: S, SO, SO_2, O, and NR^6; wherein said alkenyl, alkynyl, alkyl, aryl, heteroaryl or OR^5 are optional substituted with, hydrido, halogen, alkyl, hydroxyalkyl, aryl, heteroaryl, haloalkyl, $COCF_3$, CN, NO_2, OR^5, $OCOOR^5$, CO_2R^7, $CON(R^6)R^7$, COR^6, SR^6, SOR^6, SO_2R^6, NR^6R^7, NR^6COR^7, NR^6CONHR^7, $NR^6SO_2R^7$, $NR^6SO_2NHR^7$, and $SO_2N(R^6)R^7$ wherein R^6 and R^7 may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from the group consisting of: S, SO, SO_2, O, and NR^6;

$\mathbf{R^2}$ is selected from the group consisting of: halogen, hydrido, hydroxyalkyl, alkyl, OR^6, CN, NO_2, SR^6, NHR^6, $CON(R^6)R^7$, $NHCONHR^6$, CO_2H, and haloalkyl;

$\mathbf{R^1}$ and $\mathbf{R^2}$ may be taken together to form a 5 to 7 membered saturated or unsaturated carbocyclic ring optionally containing 0 to 3 heteroatoms selected from the group consisting of: N, O, or S, and wherein said ring is optionally substituted with R^1;

R^3 is $CONHR^{16}$;

R^4 is selected from the group consisting of: halogen, alkylsulfinyl, alkylsulfonyl, cyano, alkoxycarbonyl, alkyl, haloalkyl, hydrido, hydroxyalkyl, haloalkoxy, heterocyclic, nitro, acylamino, aryl, heteroaryl, and alkenyl, OR^{13}, SR^8, $SO_2N(R^8)R^{8'}$, NHR^9, $NHCOR^9$, NR^9COR^9, $NHCO(OR^9)$, $NR^9CO(OR^9)$, $NR^8SO_2R^{10}$, $NHSO_2N(R^{10})R^{10'}$, $NR^6CON(R^{10})R^{10'}$, COR^9, CO_2R^8, $CON(R^8)R^{8'}$, wherein R^8 and $R^{8'}$ may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from S, SO, SO_2, O, N, and NR^6, and wherein R^{10} and $R^{10'}$ may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from S, SO, SO_2, O, N, and NR^6 wherein said aryl, heterocyclic, heteroaryl, or alkenyl are optionally substituted with R^9;

R^5 is selected from the group consisting of: hydrido, alkyl, aryl, arylalkyl, heteroaryl, heterocyclicalkyl, and heteroarylalkyl, wherein aryl, alkyl, arylalkyl, heteroaryl, heterocyclicalkyl, or heteroarylalkyl are optionally substituted with one or more radicals selected from the group consisting of: OR^{14}, $N(R^{14})R^{14'}$, and glycols;

R^6 is independently selected from the group consisting of: hydrido, aryl, heteroaryl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, heterocyclicalkyl, and heterocyclic;

R^7 is independently selected from the group consisting of: hydrido, aryl, heteroaryl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, heterocyclicalkyl, and heterocyclic;

R^8 is independently selected from the group consisting of: hydrido, aryl, heteroaryl, arylalkyl, heterocyclic, haloalkyl, arylalkylamino, alkylaminoalkyl, dialkylaminoalkyl, alkyl, alkenyl, alkynyl, heteroarylalkyl, and heterocyclicalkyl;

$R^{8'}$ is independently selected from the group consisting of: hydrido, aryl, heteroaryl, arylalkyl, heterocyclic, haloalkyl, arylalkylamino, alkylaminoalkyl, dialkylaminoalkyl, alkyl, alkenyl, alkynyl, heteroarylalkyl, and heterocyclicalkyl;

R^9 is independently selected from the group consisting of: hydrido, lower alkyl, aryl, heteroaryl, arylalkyl, heterocyclic, cycloalkyl, heterocyclicalkyl, haloalkyl, arylalkylamino, amino, aminoalkyl, aminoacyl, nitro, azido, and heteroarylalkyl, wherein alkyl, aryl, heteroaryl, aminoalkyl, or arylalkyl are optionally substituted with one or more radical selected from the group consisting of: alkylsulfonamide, sulfamyl, alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, aminoalkyl, alkylaminoalkyl, alkoxy, halogen, acyloxy, oxy, formyl, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, nitro, azido, benzyloxy, dialkylaminoacyl, thioalkyl, aminoacyloxy, thiocyanate, isothiocyanate, alkyldioxy, hydroxyalkyl, alkylamino, alkyloxycarbonyl, alkoxyalkyl, alkenylamino, alkynylamino, alkenyl, alkynyl, dialkylaminoalkyloxy, and heterocyclic optionally substituted with alkyl, alkylamino, aminoalkyl, hydroxyalkyl, and alkylaminoalkyl;

R^{10} is independently selected from the group consisting of: hydrido, lower alkyl, heteroaryl, heterocyclic, haloalkyl, arylalkylamino, heteroarylalkyl, aryl, and arylalkyl, wherein aryl, heteroaryl, heterocyclic, or arylalkyl are optionally substituted with one or more radical selected from alkyl, alkoxy, halogen, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, benzyloxy, dialkylaminoalkyloxy, and heterocyclic,

$R^{10'}$ is independently selected from the group consisting of: hydrido, lower alkyl, heteroaryl, heterocyclic, haloalkyl, arylalkylamino, heteroarylalkyl, aryl, and arylalkyl, wherein aryl, heteroaryl, heterocyclic, or arylalkyl are optionally substituted with one or more radical selected from alkyl, alkoxy, halogen, haloalkyl, cyano,

haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, benzyloxy, dialkylaminoalkyloxy, and heterocyclic,

R^{11} is hydrido;

R^{12} is selected from the group consisting of: hydrido, halogen, alkyl, and alkoxy;

R^{13} is selected from the group consisting of: hydrido, alkyl, aryl, arylalkyl, heteroaryl, heterocyclicalkyl, and heteroarylalkyl, wherein aryl, alkyl, arylalkyl, heteroaryl, heterocyclicalkyl, or heteroarylalkyl are optionally substituted with one or more radicals selected from the group consisting of: OR^{14}, $N(R^{14})R^{14'}$, and glycols;

R^{14} is independently selected from the group consisting of: hydrido, and lower alkyl;

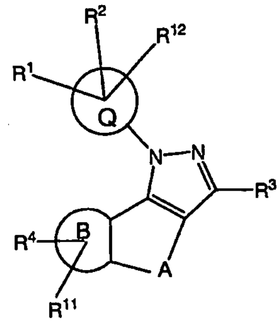
R$^{14'}$ is independently selected from the group consisting of: hydrido, and lower alkyl;

R^{15} is selected from the group consisting of: hydrido, halogen, alkyl, cycloalkyl, aryl, haloalkyl, heteroaryl, heterocyclic, alkylalkene, alkylalkyne, hydroxy, hydroxyalkyl, alkylhydroxy, amino, aminoalkyl, alkylamino, alkylaminoalkyl, alkylhydroxyalkyl, nitro, cyano, alkylthio, alkylsulfinyl, and alkylsulfonyl; wherein aryl or arylalkyl are optionally substituted with one or more radical selected from alkyl, alkoxy, halo, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, benzyloxy, dialkylaminoalkyloxy, heterocyclic; and

R^{16} is independently selected from the group consisting of: hydrido, aryl, arylalkyl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkoxy, and alkoxyalkyl;

or isomers, tautomers, carriers, esters, prodrugs, pharmaceutically acceptable salts thereof.

6. The compound of claim 3



wherein

A is $(CH_2)_m$; wherein each CH_2 may be independently substituted with one or more substitution selected from the group consisting of: hydroxy, halo, alkoxy, lower alkyl, amino, aminoalkyl, alkylamino, alkenyl, and alkynyl;

m is 0 to 8;

Q is a 5 or 6 membered heteroaryl, or aryl, optionally saturated, or optionally substituted with R^1, R^2, or R^{12};

B is an aromatic heterocyclic;

$\mathbf{R^1}$ is selected from the group consisting of: hydrido, halogen, alkyl, aryl, heteroaryl, alkenyl, alkynyl, haloalkyl, CN, NO_2, OR^5, $OCOOR^5$, CO_2R^7, $CON(R^6)R^7$, COR^6, SR^6, SOR^6, SO_2R^6, NR^6R^7, NR^6COR^7, NR^6CONHR^7, $NR^6SO_2R^7$, $NR^6SO_2NHR^7$, and $SO_2N(R^6)R^7$ wherein R^6 and R^7 may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from the group consisting of: S, SO, SO_2, O, and NR^6; wherein said alkenyl, alkynyl, alkyl, aryl, heteroaryl or OR^5 are optional substituted with, hydrido, halogen, alkyl, hydroxyalkyl, aryl, heteroaryl, haloalkyl, $COCF_3$, CN, NO_2, OR^5, $OCOOR^5$, CO_2R^7, $CON(R^6)R^7$, COR^6, SR^6, SOR^6, SO_2R^6, NR^6R^7, NR^6COR^7, NR^6CONHR^7, $NR^6SO_2R^7$, $NR^6SO_2NHR^7$, and $SO_2N(R^6)R^7$ wherein R^6 and R^7 may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted

heteroatoms selected from the group consisting of: S, SO, SO_2, O, and NR^6;

R^2 is selected from the group consisting of: halogen, hydrido, hydroxyalkyl, alkyl, OR^6, CN, NO_2, SR^6, NHR^6, $CON(R^6)R^7$, $NHCONHR^6$, CO_2H, and haloalkyl;

R^1 and **R^2** may be taken together to form a 5 to 7 membered saturated or unsaturated carbocyclic ring optionally containing 0 to 3 heteroatoms selected from the group consisting of: N, O, or S, and wherein said ring is optionally substituted with R^1;

R^3 is $CONHR^{16}$;

R^4 is selected from the group consisting of: halogen, alkylsulfinyl, alkylsulfonyl, cyano, alkoxycarbonyl, alkyl, haloalkyl, hydrido, hydroxyalkyl, haloalkoxy, heterocyclic, nitro, acylamino, aryl, heteroaryl, and alkenyl, OR^{13}, SR^8, $SO_2N(R^8)R^{8'}$, NHR^9, $NHCOR^9$, NR^9COR^9, $NHCO(OR^9)$, $NR^9CO(OR^9)$, $NR^8SO_2R^{10}$, $NHSO_2N(R^{10})R^{10'}$, $NR^6CON(R^{10})R^{10'}$, COR^9, CO_2R^8, $CON(R^8)R^{8'}$, wherein R^8 and $R^{8'}$ may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from S, SO, SO_2, O, N, and NR^6, and wherein R^{10} and $R^{10'}$ may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from S, SO, SO_2, O, N, and NR^6 wherein said aryl, heterocyclic, heteroaryl, or alkenyl are optionally substituted with R^9;

R^5 is selected from the group consisting of: hydrido, alkyl, aryl, arylalkyl, heteroaryl, heterocyclicalkyl, and heteroarylalkyl, wherein aryl, alkyl, arylalkyl, heteroaryl, heterocyclicalkyl, or heteroarylalkyl are optionally substituted with one or more radicals selected from the group consisting of: OR^{14}, $N(R^{14})R^{14'}$, and glycols;

R^6 is independently selected from the group consisting of: hydrido, aryl, heteroaryl, lower alkyl, haloalkyl, alkenyl, alkynyl,

hydroxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, heterocyclicalkyl, and heterocyclic;

R^{7} is independently selected from the group consisting of: hydrido, aryl, heteroaryl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, heterocyclicalkyl, and heterocyclic;

R^{8} is independently selected from the group consisting of: hydrido, aryl, heteroaryl, arylalkyl, heterocyclic, haloalkyl, arylalkylamino, alkylaminoalkyl, dialkylaminoalkyl, alkyl, alkenyl, alkynyl, heteroarylalkyl, and heterocyclicalkyl;

R$^{8'}$ is independently selected from the group consisting of: hydrido, aryl, heteroaryl, arylalkyl, heterocyclic, haloalkyl, arylalkylamino, alkylaminoalkyl, dialkylaminoalkyl, alkyl, alkenyl, alkynyl, heteroarylalkyl, and heterocyclicalkyl;

R^{9} is independently selected from the group consisting of: hydrido, lower alkyl, aryl, heteroaryl, arylalkyl, heterocyclic, cycloalkyl, heterocyclicalkyl, haloalkyl, arylalkylamino, amino, aminoalkyl, aminoacyl, nitro, azido, and heteroarylalkyl, wherein alkyl, aryl, heteroaryl, aminoalkyl, or arylalkyl are optionally substituted with one or more radical selected from the group consisting of: alkylsulfonamide, sulfamyl, alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, aminoalkyl, alkylaminoalkyl, alkoxy, halogen, acyloxy, oxy, formyl, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, nitro, azido, benzyloxy, dialkylaminoacyl, thioalkyl, aminoacyloxy, thiocyanate, isothiocyanate, alkyldioxy, hydroxyalkyl, alkylamino, alkyloxycarbonyl, alkoxyalkyl, alkenylamino, alkynylamino, alkenyl, alkynyl, dialkylaminoalkyloxy, and heterocyclic optionally substituted with alkyl, alkylamino, aminoalkyl, hydroxyalkyl, and alkylaminoalkyl;

R^{10} is independently selected from the group consisting of: hydrido, lower alkyl, heteroaryl, heterocyclic, haloalkyl, arylalkylamino,

heteroarylalkyl, aryl, and arylalkyl, wherein aryl, heteroaryl, heterocyclic, or arylalkyl are optionally substituted with one or more radical selected from alkyl, alkoxy, halogen, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, benzyloxy, dialkylaminoalkyloxy, and heterocyclic,

$R^{10'}$ is independently selected from the group consisting of: hydrido, lower alkyl, heteroaryl, heterocyclic, haloalkyl, arylalkylamino, heteroarylalkyl, aryl, and arylalkyl, wherein aryl, heteroaryl, heterocyclic, or arylalkyl are optionally substituted with one or more radical selected from alkyl, alkoxy, halogen, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, benzyloxy, dialkylaminoalkyloxy, and heterocyclic,

R^{11} is hydrido;

R^{12} is hydrido;

R^{13} is selected from the group consisting of: hydrido, alkyl, aryl, arylalkyl, heteroaryl, heterocyclicalkyl, and heteroarylalkyl, wherein aryl, alkyl, arylalkyl, heteroaryl, heterocyclicalkyl, or heteroarylalkyl are optionally substituted with one or more radicals selected from the group consisting of: OR^{14}, $N(R^{14})R^{14'}$, and glycols;

R^{14} is independently selected from the group consisting of: hydrido, and lower alkyl;

$R^{14'}$ is independently selected from the group consisting of: hydrido, and lower alkyl;

R^{15} is selected from the group consisting of: hydrido, halogen, alkyl, cycloalkyl, aryl, haloalkyl, heteroaryl, heterocyclic, alkylalkene, alkylalkyne, hydroxy, hydroxyalkyl, alkylhydroxy, amino, aminoalkyl, alkylamino, alkylaminoalkyl, alkylhydroxyalkyl, nitro, cyano, alkylthio, alkylsulfinyl, and alkylsulfonyl; wherein aryl or arylalkyl are optionally substituted with one or more radical selected from alkyl, alkoxy, halo, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, benzyloxy, dialkylaminoalkyloxy, heterocyclic; and

R^{16} is independently selected from the group consisting of: hydrido, aryl, arylalkyl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkoxy, and alkoxyalkyl;

or isomers, tautomers, carriers, esters, prodrugs, pharmaceutically acceptable salts thereof.

7. The compound of claim 4

wherein

A is $(CH_2)_m$, wherein each CH_2 may be independently substituted with one or more substitution selected from the group consisting of: hydroxy, halo, alkoxy, lower alkyl, amino, aminoalkyl, alkylamino, alkenyl, and alkynyl;

m is 1 or 2;

B is a 5 or 6 membered aromatic heterocyclic;

Q is a 5 or 6 membered heteroaryl, or aryl, optionally saturated, or optionally substituted with R^1;

B is an aromatic heterocyclic;

R^1 is selected from the group consisting of: hydrido, halogen, alkyl, aryl, heteroaryl, alkenyl, alkynyl, haloalkyl, CN, NO_2, OR^5, $OCOOR^5$, CO_2R^7, $CON(R^6)R^7$, COR^6, SR^6, SOR^6, SO_2R^6, NR^6R^7, NR^6COR^7, NR^6CONHR^7, $NR^6SO_2R^7$, $NR^6SO_2NHR^7$, and $SO_2N(R^6)R^7$ wherein R^6 and R^7 may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from the group consisting of: S, SO, SO_2, O, and NR^6; wherein said alkenyl, alkynyl, alkyl, aryl, heteroaryl or OR^5 are optional substituted with, hydrido, halogen, alkyl, hydroxyalkyl, aryl, heteroaryl, haloalkyl, $COCF_3$, CN, NO_2, OR^5, $OCOOR^5$, CO_2R^7, $CON(R^6)R^7$, COR^6, SR^6, SOR^6, SO_2R^6, NR^6R^7, NR^6COR^7, NR^6CONHR^7, $NR^6SO_2R^7$, $NR^6SO_2NHR^7$, and $SO_2N(R^6)R^7$ wherein R^6 and R^7 may be taken together to form a 3-7 membered

carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from the group consisting of: S, SO, SO_2, O, and NR^6;

R^2 is hydrido;

R^3 is $CONHR^{16}$;

R^4 is selected from the group consisting of: halogen, alkylsulfinyl, alkylsulfonyl, cyano, alkoxycarbonyl, alkyl, haloalkyl, hydrido, hydroxyalkyl, haloalkoxy, heterocyclic, nitro, acylamino, aryl, heteroaryl, and alkenyl, OR^{13}, SR^8, $SO_2N(R^8)R^{8'}$, NHR^9, $NHCOR^9$, NR^9COR^9, $NHCO(OR^9)$, $NR^9CO(OR^9)$, $NR^8SO_2R^{10}$, $NHSO_2N(R^{10})R^{10'}$, $NR^6CON(R^{10})R^{10'}$, COR^9, CO_2R^8, $CON(R^8)R^{8'}$, wherein R^8 and $R^{8'}$ may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from S, SO, SO_2, O, N, and NR^6, and wherein R^{10} and $R^{10'}$ may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from S, SO, SO_2, O, N, and NR^6 wherein said aryl, heterocyclic, heteroaryl, or alkenyl are optionally substituted with R^9;

R^5 is selected from the group consisting of: hydrido, alkyl, aryl, arylalkyl, heteroaryl, heterocyclicalkyl, and heteroarylalkyl, wherein aryl, alkyl, arylalkyl, heteroaryl, heterocyclicalkyl, or heteroarylalkyl are optionally substituted with one or more radicals selected from the group consisting of: OR^{14}, $N(R^{14})R^{14'}$, and glycols;

R^6 is independently selected from the group consisting of: hydrido, aryl, heteroaryl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, heterocyclicalkyl, and heterocyclic;

R^7 is independently selected from the group consisting of: hydrido, aryl, heteroaryl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, heterocyclicalkyl, and heterocyclic;

R^8 is independently selected from the group consisting of: hydrido, aryl, heteroaryl, arylalkyl, heterocyclic, haloalkyl, arylalkylamino, alkylaminoalkyl, dialkylaminoalkyl, alkyl, alkenyl, alkynyl, heteroarylalkyl, and heterocyclicalkyl;

$R^{8'}$ is independently selected from the group consisting of: hydrido, aryl, heteroaryl, arylalkyl, heterocyclic, haloalkyl, arylalkylamino, alkylaminoalkyl, dialkylaminoalkyl, alkyl, alkenyl, alkynyl, heteroarylalkyl, and heterocyclicalkyl;

R^9 is independently selected from the group consisting of: hydrido, lower alkyl, aryl, heteroaryl, arylalkyl, heterocyclic, cycloalkyl, heterocyclicalkyl, haloalkyl, arylalkylamino, amino, aminoalkyl, aminoacyl, nitro, azido, and heteroarylalkyl, wherein alkyl, aryl, heteroaryl, aminoalkyl, or arylalkyl are optionally substituted with one or more radical selected from the group consisting of: alkylsulfonamide, sulfamyl, alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, aminoalkyl, alkylaminoalkyl, alkoxy, halogen, acyloxy, oxy, formyl, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, nitro, azido, benzyloxy, dialkylaminoacyl, thioalkyl, aminoacyloxy, thiocyanate, isothiocyanate, alkyldioxy, hydroxyalkyl, alkylamino, alkyloxycarbonyl, alkoxyalkyl, alkenylamino, alkynylamino, alkenyl, alkynyl, dialkylaminoalkyloxy, and heterocyclic optionally substituted with alkyl, alkylamino, aminoalkyl, hydroxyalkyl, and alkylaminoalkyl;

R^{10} is independently selected from the group consisting of: hydrido, lower alkyl, heteroaryl, heterocyclic, haloalkyl, arylalkylamino, heteroarylalkyl, aryl, and arylalkyl, wherein aryl, heteroaryl, heterocyclic, or arylalkyl are optionally substituted with one or more radical selected from alkyl, alkoxy, halogen, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, benzyloxy, dialkylaminoalkyloxy, and heterocyclic,

R$^{10'}$ is independently selected from the group consisting of: hydrido, lower alkyl, heteroaryl, heterocyclic, haloalkyl, arylalkylamino, heteroarylalkyl, aryl, and arylalkyl, wherein aryl, heteroaryl, heterocyclic, or arylalkyl are optionally substituted with one or more radical selected from alkyl, alkoxy, halogen, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, benzyloxy, dialkylaminoalkyloxy, and heterocyclic,

R^{11} is selected from the group consisting of hydrido, halo, CF_3, CN, CO_2R^5, and $CONH_2$;

R^{12} is hydrido;

R^{13} is selected from the group consisting of: hydrido, alkyl, aryl, arylalkyl, heteroaryl, heterocyclicalkyl, and heteroarylalkyl, wherein aryl, alkyl, arylalkyl, heteroaryl, heterocyclicalkyl, or heteroarylalkyl are optionally substituted with one or more radicals selected from the group consisting of: OR^{14}, $N(R^{14})R^{14'}$, and glycols;

R^{14} is independently selected from the group consisting of: hydrido, and lower alkyl;

R$^{14'}$ is independently selected from the group consisting of: hydrido, and lower alkyl;

R^{15} is selected from the group consisting of: hydrido, halogen, alkyl, cycloalkyl, aryl, haloalkyl, heteroaryl, heterocyclic, alkylalkene, alkylalkyne, hydroxy, hydroxyalkyl, alkylhydroxy, amino, aminoalkyl, alkylamino, alkylaminoalkyl, alkylhydroxyalkyl, nitro, cyano, alkylthio, alkylsulfinyl, and alkylsulfonyl; wherein aryl or arylalkyl are optionally substituted with one or more radical selected from alkyl, alkoxy, halo, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, benzyloxy, dialkylaminoalkyloxy, heterocyclic; and

R^{16} is independently selected from the group consisting of: hydrido, aryl, arylalkyl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkoxy, and alkoxyalkyl;

or isomers, tautomers, carriers, esters, prodrugs, pharmaceutically acceptable salts thereof.

8. The compound of claim 7

wherein

A is $(CH_2)_m$, wherein each CH_2 may be independently substituted with one or more substitution selected from the group consisting of: hydroxy, halo, alkoxy, lower alkyl, amino, aminoalkyl, alkylamino, alkenyl, and alkynyl;

m is 2;

B is a 5 or 6 membered aromatic heterocyclic;

$\mathbf{R^1}$ is selected from the group consisting of SO_2NH_2, $SO_2N(R^6)_2$, and SO_2R^6;

$\mathbf{R^3}$ is $CONH_2$;

$\mathbf{R^4}$ is selected from the group consisting of: halogen, alkylsulfinyl, alkylsulfonyl, cyano, alkoxycarbonyl, alkyl, haloalkyl, hydrido, hydroxyalkyl, haloalkoxy, heterocyclic, nitro, acylamino, aryl, heteroaryl, and alkenyl, OR^{13}, SR^8, $SO_2N(R^8)R^{8'}$, NHR^9, $NHCOR^9$, NR^9COR^9, $NHCO(OR^9)$, $NR^9CO(OR^9)$, $NR^8SO_2R^{10}$, $NHSO_2N(R^{10})R^{10'}$, $NR^6CON(R^{10})R^{10'}$, COR^9, CO_2R^8, $CON(R^8)R^{8'}$, wherein R^8 and $R^{8'}$ may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from S, SO, SO_2, O, N, and NR^6, and wherein R^{10} and $R^{10'}$ may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from S, SO, SO_2, O, N, and NR^6 wherein said aryl, heterocyclic, heteroaryl, or alkenyl are optionally substituted with R^9;

$\mathbf{R^5}$ is selected from the group consisting of: hydrido, alkyl, aryl, arylalkyl, heteroaryl, heterocyclicalkyl, and heteroarylalkyl, wherein aryl, alkyl, arylalkyl, heteroaryl, heterocyclicalkyl, or heteroarylalkyl

are optionally substituted with one or more radicals selected from the group consisting of: OR^{14}, $N(R^{14})R^{14'}$, and glycols;

$\mathbf{R^6}$ is independently selected from the group consisting of: hydrido, aryl, heteroaryl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, heterocyclicalkyl, and heterocyclic;

$\mathbf{R^7}$ is independently selected from the group consisting of: hydrido, aryl, heteroaryl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, heterocyclicalkyl, and heterocyclic;

$\mathbf{R^8}$ is independently selected from the group consisting of: hydrido, aryl, heteroaryl, arylalkyl, heterocyclic, haloalkyl, arylalkylamino, alkylaminoalkyl, dialkylaminoalkyl, alkyl, alkenyl, alkynyl, heteroarylalkyl, and heterocyclicalkyl;

$\mathbf{R^{8'}}$ is independently selected from the group consisting of: hydrido, aryl, heteroaryl, arylalkyl, heterocyclic, haloalkyl, arylalkylamino, alkylaminoalkyl, dialkylaminoalkyl, alkyl, alkenyl, alkynyl, heteroarylalkyl, and heterocyclicalkyl;

$\mathbf{R^9}$ is independently selected from the group consisting of: hydrido, lower alkyl, aryl, heteroaryl, arylalkyl, heterocyclic, cycloalkyl, heterocyclicalkyl, haloalkyl, arylalkylamino, amino, aminoalkyl, aminoacyl, nitro, azido, and heteroarylalkyl, wherein alkyl, aryl, heteroaryl, aminoalkyl, or arylalkyl are optionally substituted with one or more radical selected from the group consisting of: alkylsulfonamide, sulfamyl, alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, aminoalkyl, alkylaminoalkyl, alkoxy, halogen, acyloxy, oxy, formyl, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, nitro, azido, benzyloxy, dialkylaminoacyl, thioalkyl, aminoacyloxy, thiocyanate, isothiocyanate, alkyldioxy, hydroxyalkyl, alkylamino, alkyloxycarbonyl, alkoxyalkyl, alkenylamino, alkynylamino, alkenyl, alkynyl, dialkylaminoalkyloxy, and heterocyclic optionally

substituted with alkyl, alkylamino, aminoalkyl, hydroxyalkyl, and alkylaminoalkyl;

R^{10} is independently selected from the group consisting of: hydrido, lower alkyl, heteroaryl, heterocyclic, haloalkyl, arylalkylamino, heteroarylalkyl, aryl, and arylalkyl, wherein aryl, heteroaryl, heterocyclic, or arylalkyl are optionally substituted with one or more radical selected from alkyl, alkoxy, halogen, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, benzyloxy, dialkylaminoalkyloxy, and heterocyclic,

R$^{10'}$ is independently selected from the group consisting of: hydrido, lower alkyl, heteroaryl, heterocyclic, haloalkyl, arylalkylamino, heteroarylalkyl, aryl, and arylalkyl, wherein aryl, heteroaryl, heterocyclic, or arylalkyl are optionally substituted with one or more radical selected from alkyl, alkoxy, halogen, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, benzyloxy, dialkylaminoalkyloxy, and heterocyclic,

R^{11} is selected from the group consisting of hydrido, halo, CF_3, CN, CO_2R^5, and $CONH_2$;

R^{12} is hydrido;

R^{13} is selected from the group consisting of: hydrido, alkyl, aryl, arylalkyl, heteroaryl, heterocyclicalkyl, and heteroarylalkyl, wherein aryl, alkyl, arylalkyl, heteroaryl, heterocyclicalkyl, or heteroarylalkyl are optionally substituted with one or more radicals selected from the group consisting of: OR^{14}, $N(R^{14})R^{14'}$, and glycols;

R^{14} is independently selected from the group consisting of: hydrido, and lower alkyl;

R$^{14'}$ is independently selected from the group consisting of: hydrido, and lower alkyl;

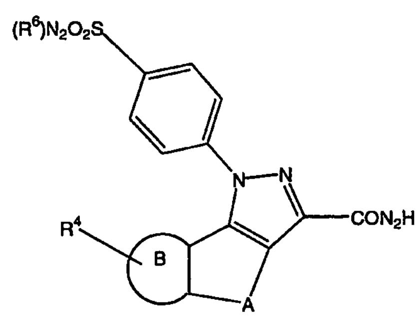
R^{15} is selected from the group consisting of: hydrido, halogen, alkyl, cycloalkyl, aryl, haloalkyl, heteroaryl, heterocyclic, alkylalkene, alkylalkyne, hydroxy, hydroxyalkyl, alkylhydroxy, amino, aminoalkyl, alkylamino, alkylaminoalkyl, alkylhydroxyalkyl, nitro,

cyano, alkylthio, alkylsulfinyl, and alkylsulfonyl; wherein aryl or arylalkyl are optionally substituted with one or more radical selected from alkyl, alkoxy, halo, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, benzyloxy, dialkylaminoalkyloxy, heterocyclic; and

R^{16} is independently selected from the group consisting of: hydrido, aryl, arylalkyl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkoxy, and alkoxyalkyl;

or isomers, tautomers, carriers, esters, prodrugs, pharmaceutically acceptable salts thereof.

9. The compound of claim 6 of the formula



wherein

A is $(CH_2)_m$;

m is 1 or 2;

B is a 5 or 6 membered aromatic heterocyclic;

R^4 is selected from the group consisting of: halogen, alkylsulfinyl, alkylsulfonyl, cyano, alkoxycarbonyl, alkyl, haloalkyl, hydrido, hydroxyalkyl, haloalkoxy, heterocyclic, nitro, acylamino, aryl, heteroaryl, and alkenyl, OR^{13}, SR^8, $SO_2N(R^8)R^{8'}$, NHR^9, $NHCOR^9$, NR^9COR^9, $NHCO(OR^9)$, $NR^9CO(OR^9)$, $NR^8SO_2R^{10}$, $NHSO_2N(R^{10})R^{10'}$, $NR^6CON(R^{10})R^{10'}$, COR^9, CO_2R^8, $CON(R^8)R^{8'}$, wherein R^8 and $R^{8'}$ may be taken together to form a 3-7 membered

carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from S, SO, SO_2, O, N, and NR^6, and wherein R^{10} and $R^{10'}$ may be taken together to form a 3-7 membered carbocyclic ring having 1 to 3 substituted or unsubstituted heteroatoms selected from S, SO, SO_2, O, N, and NR^6 wherein said aryl, heterocyclic, heteroaryl, or alkenyl are optionally substituted with R^9;

$\mathbf{R^8}$ is independently selected from the group consisting of: hydrido, aryl, heteroaryl, arylalkyl, heterocyclic, haloalkyl, arylalkylamino, alkylaminoalkyl, dialkylaminoalkyl, alkyl, alkenyl, alkynyl, heteroarylalkyl, and heterocyclicalkyl;

$\mathbf{R^{8'}}$ is independently selected from the group consisting of: hydrido, aryl, heteroaryl, arylalkyl, heterocyclic, haloalkyl, arylalkylamino, alkylaminoalkyl, dialkylaminoalkyl, alkyl, alkenyl, alkynyl, heteroarylalkyl, and heterocyclicalkyl;

$\mathbf{R^9}$ is independently selected from the group consisting of: hydrido, lower alkyl, aryl, heteroaryl, arylalkyl, heterocyclic, cycloalkyl, heterocyclicalkyl, haloalkyl, arylalkylamino, amino, aminoalkyl, aminoacyl, nitro, azido, and heteroarylalkyl, wherein alkyl, aryl, heteroaryl, aminoalkyl, or arylalkyl are optionally substituted with one or more radical selected from the group consisting of: alkylsulfonamide, sulfamyl, alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, aminoalkyl, alkylaminoalkyl, alkoxy, halogen, acyloxy, oxy, formyl, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, nitro, azido, benzyloxy, dialkylaminoacyl, thioalkyl, aminoacyloxy, thiocyanate, isothiocyanate, alkyldioxy, hydroxyalkyl, alkylamino, alkyloxycarbonyl, alkoxyalkyl, alkenylamino, alkynylamino, alkenyl, alkynyl, dialkylaminoalkyloxy, and heterocyclic optionally substituted with alkyl, alkylamino, aminoalkyl, hydroxyalkyl, and alkylaminoalkyl;

R^{10} is independently selected from the group consisting of: hydrido, lower alkyl, heteroaryl, heterocyclic, haloalkyl, arylalkylamino, heteroarylalkyl, aryl, and arylalkyl, wherein aryl, heteroaryl, heterocyclic, or arylalkyl are optionally substituted with one or more radical selected from alkyl, alkoxy, halogen, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, benzyloxy, dialkylaminoalkyloxy, and heterocyclic,

$R^{10'}$ is independently selected from the group consisting of: hydrido, lower alkyl, heteroaryl, heterocyclic, haloalkyl, arylalkylamino, heteroarylalkyl, aryl, and arylalkyl, wherein aryl, heteroaryl, heterocyclic, or arylalkyl are optionally substituted with one or more radical selected from alkyl, alkoxy, halogen, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, benzyloxy, dialkylaminoalkyloxy, and heterocyclic,

R^{13} is selected from the group consisting of: hydrido, alkyl, aryl, arylalkyl, heteroaryl, heterocyclicalkyl, and heteroarylalkyl, wherein aryl, alkyl, arylalkyl, heteroaryl, heterocyclicalkyl, or heteroarylalkyl are optionally substituted with one or more radicals selected from the group consisting of: OR^{14}, $N(R^{14})R^{14'}$, and glycols;

R^{14} is independently selected from the group consisting of: hydrido, and lower alkyl;

$R^{14'}$ is independently selected from the group consisting of: hydrido, and lower alkyl;

R^{15} is selected from the group consisting of: hydrido, halogen, alkyl, cycloalkyl, aryl, haloalkyl, heteroaryl, heterocyclic, alkylalkene, alkylalkyne, hydroxy, hydroxyalkyl, alkylhydroxy, amino, aminoalkyl, alkylamino, alkylaminoalkyl, alkylhydroxyalkyl, nitro, cyano, alkylthio, alkylsulfinyl, and alkylsulfonyl; wherein aryl or arylalkyl are optionally substituted with one or more radical selected from alkyl, alkoxy, halo, haloalkyl, cyano, haloalkoxy, acyl, carboxyl, hydroxy, hydroxyalkyloxy, phenoxy, benzyloxy, dialkylaminoalkyloxy, heterocyclic; and

R^{16} is independently selected from the group consisting of: hydrido, aryl, arylalkyl, lower alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkoxy, and alkoxyalkyl;

or isomers, tautomers, carriers, esters, prodrugs, pharmaceutically acceptable salts thereof.

10. The compound of 3, 4, 5, 6, or 7 wherein R^3 is $CONH_2$.

11. The compound of claim 3, 4, 5, 6, 7, 8, or 9 wherein **B** is selected from the group consisting of: thiophene, pyrrole, imidazole, pyrazole, pyridazine, pyrimidine, pyridine, and pyrazine.

12. The compound of claim 10 wherein **B** is selected from the group consisting of: thiophene, pyrrole, imidazole, pyrazole, pyridazine, pyrimidine, pyridine, and pyrazine.

13. The compound of claim 9 selected from the group consisting of:

ethyl 1-[4-(aminosulfonyl)phenyl]-6-benzyl-1,4,5,6-tetrahydropyrrolo[2,3-g]indazole-3-carboxylate,
1-[4-(aminosulfonyl)phenyl]-6-benzyl-1,4,5,6-tetrahydropyrrolo[2,3-g]indazole-3-carboxamide,
ethyl 1-[4-(aminosulfonyl)phenyl]-6-benzyl-1,4,5,6-tetrahydropyrazolo[3,4-e]indazole-3-carboxylate,
1-[4-(aminosulfonyl)phenyl]-6-benzyl-1,4,5,6-tetrahydropyrazolo[3,4-e]indazole-3-carboxamide,
ethyl 1-[4-(aminosulfonyl)phenyl]-1,4,5,6-tetrahydropyrazolo[3,4-e]indazole-3-carboxylate,
1-[4-(aminosulfonyl)phenyl]-1,4,5,6-tetrahydropyrazolo[3,4-e]indazole-3-carboxamide,

ethyl 1-[4-(aminosulfonyl)phenyl]-4,5-dihydro-1H-thieno[2,3-g]indazole-3-carboxylate,
1-[4-(aminosulfonyl)phenyl]-4,5-dihydro-1H-thieno[2,3-g]indazole-3-carboxamide,
1-[4-(aminosulfonyl)phenyl]-4,5-dihydro-1H-pyrazolo[3,4-f]isoquinoline-3-carboxamide,
1-[4-(aminosulfonyl)phenyl]-1,4,5,8-tetrahydropyrazolo[4,3-g]indazole-3-carboxamide,
8-amino-1-[4-(aminosulfonyl)phenyl]-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide,
8-Chloro-1-(4-fluorophenyl)-4,5-dihydro-1H-pyrazolo[4,3-h]quinoline-3-carboxamide,
1-(4-Fluorophenyl)-N-(4-methoxybenzyl)-8-[(4-methoxybenzyl)amino]-4,5-dihydro-1H-pyrazolo[4,3-h]quinoline-3-carboxamide,
8-[(3-chloroisonicotinoyl)amino]-1-(4-fluorophenyl)-4,5-dihydro-1H-pyrazolo[4,3-h]quinoline-3-carboxamide,
8-{[(2-chloropyridin-3-yl)carbonyl]amino}-1-(4-fluorophenyl)-4,5-dihydro-1H-pyrazolo[4,3-h]quinoline-3-carboxamide, and
8-{[5-chloro-2-(4-methylpiperazin-1-yl)isonicotinoyl]amino}-1-(4-fluorophenyl)-4,5-dihydro-1H-pyrazolo[4,3-h]quinoline-3-carboxamide.

14. A composition comprising the compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, or 13 and at least one pharmaceutically acceptable carrier.

15. A composition comprising the compound of claim 10 and at least one pharmaceutically acceptable carrier.

16. A composition comprising the compound of claim 11 and at least one pharmaceutically acceptable carrier.

17. A composition comprising the compound of claim 12 and at least one pharmaceutically acceptable carrier.

18. A method of treating cancer, inflammation or an inflammation associated disorder in a subject, said method comprising administering to the subject having or susceptible to such cancer, inflammation or inflammation associated disorder, a therapeutically-effective amount of a compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, or 13.

19. A method of treating cancer, inflammation or an inflammation associated disorder in a subject, said method comprising administering to the subject having or susceptible to such cancer, inflammation or inflammation associated disorder, a therapeutically-effective amount of a compound of claim 10.

20. A method of treating cancer, inflammation or an inflammation associated disorder in a subject, said method comprising administering to the subject having or susceptible to such cancer, inflammation or inflammation associated disorder, a therapeutically-effective amount of a compound of claim 11.

21. A method of treating cancer, inflammation or an inflammation associated disorder in a subject, said method comprising administering to the subject having or susceptible to such cancer, inflammation or inflammation associated disorder, a therapeutically-effective amount of a compound of claim 12.

22. The method of claim 21 for use in the treatment of cancer.

23. The method of claim 21 for use in the treatment of inflammation.

24. The method of claim 21 for use in the treatment of an inflammation-associated disorder.

25. The method of claim 24 wherein the inflammation-associated disorder is arthritis.

26. The method of claim 24 wherein the inflammation-associated disorder is pain

27. The method of claim 24 wherein the inflammation-associated disorder is fever.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/04844

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D231/54 C07D487/04 C07D495/04 A61K31/416 A61P35/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 09293 A (SEARLE & CO ;ROGERS KATHY L (US); TALLEY JOHN J (US); BERTENSHAW S) 28 March 1996 (1996-03-28) cited in the application page 1, line 6 - line 10 page 2, formula (I) Examples 4-5 claims 15-18	2-27

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 July 2003	25/07/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hoepfner, W

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1

Present claim 1 relates to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a limited proportion of the compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely the compounds of formula II, i.e. the worked Examples and the subject-matter of claims 2-27 as far as claim 1 is not concerned.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

Inter[redacted]nal application No.
PCT/US 03/04844

INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 18-27 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 03/04844

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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